American Journal of Obstetrics and Gynecology

VOL. 71 JANUARY, 1956 NO. 1

Original Communications

OXYGEN SATURATION DETERMINATIONS OF THE NEWBORN IN VAGINAL DELIVERY AND CESAREAN SECTION*

THADDEUS L. MONTGOMERY, M.D., ROBERT T. BRANDFASS, M.D., AND HOWARD E. FIRST, M.D., PHILADELPHIA, PA.

(From the Department of Obstetrics and Gynecology, Jefferson Medical College and Hospital)

IT IS a generally accepted observation in obstetric and pediatric circles that babies born by cesarean section do not do as well as those born by vaginal delivery.[1, 2] Apparently, for one reason or another, the respiratory mechanism of the newborn is not properly sensitized, and quite a number of neonatal deaths occur as a result of atelectasis and the development of asphyxial membranes. This circumstance is possibly not as well known to the obstetrician as it is to the nurse who attends such babies in the nursery, or to the pediatrician who has the care of the baby born by cesarean section and the unfortunate responsibility of following some cases to the autopsy table.

There have been many conjectures as to the cause of the condition, but thus far no one or several etiological factors have been definitely incriminated. The study of the condition has depended principally upon the clinical course of the disease and the findings at autopsy.

It occurred to us that the problem might be approached through a study of successive fetal oxygen saturation values following cesarean section compared with those following vaginal delivery. It was felt that such a series of determinations might show a significant difference between these two groups, inasmuch as the underlying difficulty is respiratory. If a significant difference were noted, then serial oxygen saturation determinations might be used to evaluate the efficacy of various types of anesthesia, modifications in technique of operation, or changes in procedure of handling the baby born by cesarean section.

*Presented at a meeting of the Obstetrical Society of Philadelphia, Oct. 7, 1954.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

This first paper has to do with the first question, namely, whether there is a significant difference in the course of oxygen saturation in cesarean section babies and in spontaneous delivery. Further work is in progress on methods of performing cesarean section and handling the cesarean section baby which might alter the picture.

Previous work in the field of fetal respiratory mechanism and oxygen-saturation studies has been done by Nicholson J. Eastman,[3, 4, 5] E. S. Taylor and colleagues,[7, 8, 9] and others.[6, 10] We are indebted to them and to the physiologists and chemists[11, 12] who have laid the groundwork for studies of this character.

In our own work we have followed the procedure employed by Taylor for the microchemical analysis of specimens of capillary fetal blood collected at successive intervals after delivery, and are indebted to him for valuable suggestions and advice.

Procedure

In this series of determinations, the first specimen of blood was collected 15 to 20 minutes after delivery, when pulsation of the cord had ceased, the pharynx had been aspirated, and the respiratory rhythm of the fetus well established. We had decided that we would not alter our routine management of the newborn by immediate clamping of segments of the cord after delivery, or by immediate collecting of cutaneous blood. It was felt that the other investigators had repeatedly determined the oxygen content of fetal arterial blood at the moment of delivery and this phase of the study did not require repetition.

Specimens therefore were collected from the fetal heel under anaerobic conditions by cutaneous puncture at intervals of 15 or 20 minutes, one hour, and three hours after delivery, and analyzed in the Kopp-Natelson microgasometer for oxygen content. In certain cases additional collections were made at other intervals, and 12 to 24 hours after delivery.

Upon conclusion of pulsation of the cord, blood was withdrawn from the cord vein, exposed to air until saturated with oxygen, and then analyzed in the Van Slyke-Neil apparatus for its oxygen-carrying capacity. Results were reported in percentage of oxygen saturation—the ratio of the oxygen content of the capillary heel blood to the oxygen-carrying capacity of the fetal cord blood.

Comparative analysis of a single specimen of blood in the Van Slyke-Neil apparatus and the Kop-Natelson microgasometer revealed a difference in result of not more than 0.3 volume per cent, confirming the accuracy of the microchemical procedure.[11]

The cesarean sections chosen for study were all elective procedures performed under continuous spinal anesthesia. The baby was kept at the table approximately five minutes until most of the blood had been pumped over from the placenta, and the upper air passages cleared of fluid and mucus. The baby was then handed to a pediatrician for further observation and care, and placed in an incubator or under an oxygen hood for 12 to 24 hours. Oxygen volume was maintained at approximately 40 per cent.

Results

Eight determinations were made in normal vaginal deliveries without analgesia or anesthesia (Table I). In these determinations the mean oxygen

saturation at 15 to 20 minutes was 79 per cent, the oxygen saturation at one hour after delivery was 84 per cent, the oxygen saturation three hours after delivery was 94 per cent (Fig. 1).

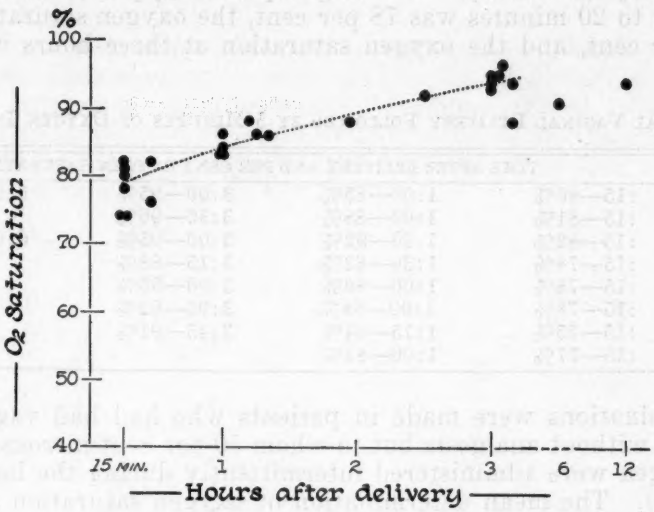


Fig. 1.—Mean curve in normal vaginal delivery.

Fig. 2.—Mean curve in normal vaginal delivery followed by five minutes of oxygen inhalation to baby.

TABLE I. NORMAL VAGINAL DELIVERY

CASE NO.	TIME AFTER DELIVERY AND PER CENT OXYGEN SATURATION				
32	:25—76%	1:55—88%	2:35—92%		
39	:25—82%	1:15—86%	3:40—94%		
47	:11—82%	1:11—88%	3:20—96%		
74	:15—81%	1:20—86%	3:40—88%	:6—91%	:12—94%
97	:15—80%	1:00—86%	3:15—95%		
98	:15—74%	1:00—83%	3:00—93%		
99	:15—74%	1:00—83%	3:00—94%		
100	:15—78%	1:00—84%	3:00—95%		

Eight determinations were made in spontaneous delivery without analgesia or anesthesia in which, in addition, 100 per cent oxygen was administered to the baby for five minutes after delivery, not because of need, but as a part of the study (Table II). In this group the oxygen saturation of the fetal blood at 15 to 20 minutes was 78 per cent, the oxygen saturation at one hour was 86 per cent, and the oxygen saturation at three hours was 93 per cent (Fig. 2).

TABLE II. NORMAL VAGINAL DELIVERY FOLLOWED BY 5 MINUTES OF OXYGEN INHALATION

CASE NO.	TIME AFTER DELIVERY AND PER CENT OXYGEN SATURATION			
105	:15—80%	1:00—85%	3:00—95%	6:00—95%
106	:15—81%	1:00—88%	3:30—96%	
107	:15—82%	1:00—92%	3:00—95%	6:00—95%
108	:15—78%	1:30—83%	3:15—88%	
110	:15—78%	1:00—86%	3:00—93%	
111	:15—78%	1:00—88%	3:00—92%	
112	:15—75%	1:15—84%	3:45—91%	
113	:15—77%	1:00—83%		

Four determinations were made in patients who had had vaginal spontaneous delivery without analgesia but to whom 50 per cent nitrous oxide and 50 per cent oxygen were administered intermittently during the last stage of labor (Table III). The mean determination of oxygen saturation at 15 minutes was 19 per cent, at one hour 84 per cent, and at three hours, 94 per cent (Fig. 3).

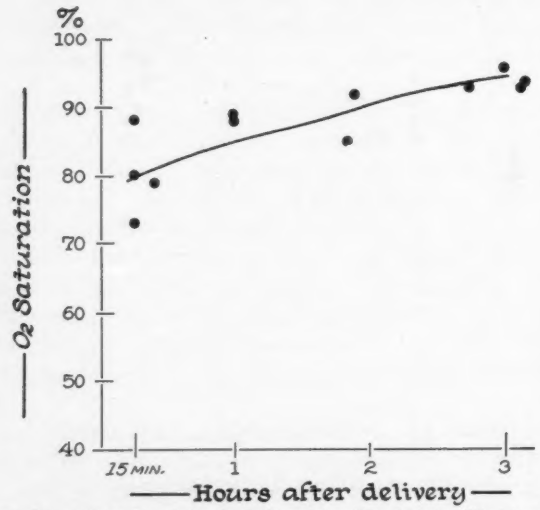


Fig. 3.—Mean curve in normal vaginal delivery with intermittent nitrous oxide and oxygen during delivery.

TABLE III. NORMAL VAGINAL DELIVERY WITH INTERMITTENT NITROUS OXIDE AND OXYGEN

CASE NO.	TIME AFTER DELIVERY AND PER CENT OXYGEN SATURATION		
36	:15—88%	1:55—92%	3:00—96%
37	:23—79%	1:00—89%	2:45—93%
103	:15—73%	1:50—85%	3:50—94%
114	:15—80%	1:00—88%	3:30—93%

Eight determinations of oxygen saturation were made in cesarean section performed under continuous spinal anesthesia as an elective procedure (Table IV). Oxygen saturation determinations in these cases revealed a per-

centage of saturation at the conclusion of 15 to 20 minutes of 68 per cent, at one hour of 76 per cent, and at three hours of 80 per cent. A determination made 24 hours later in these patients showed oxygen saturation of 88 per cent, or five points lower than the oxygen saturation at three hours in spontaneous delivery (Fig. 4).

The three curves of oxygen saturation in spontaneous delivery may be superimposed upon each other with practically no deviation (Fig. 5). It appears that neither the administration of oxygen to the baby after delivery nor the administration of 50 per cent nitrous oxide and oxygen to the mother during labor had any effect upon the rapidity of oxygen saturation of the blood of the newborn infant.

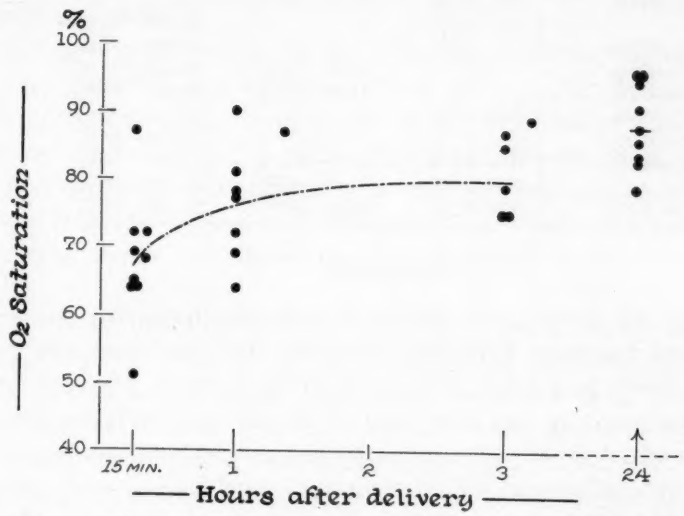


Fig. 4.—Mean curve in elective cesarean section under continuous spinal anesthesia.

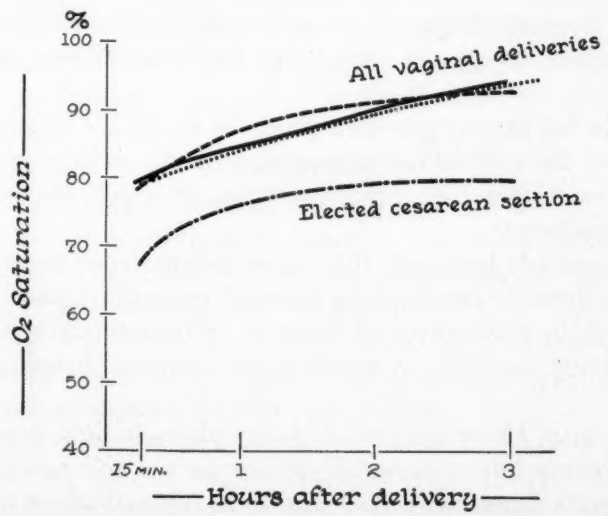


Fig. 5.—Comparison of mean curves in normal vaginal delivery and cesarean section.

The comparison of the oxygen saturation values in cesarean section with those of the 19 determinations in spontaneous delivery revealed quite decided differences in level at the fifteen-minute, one-hour, and three-hour periods

(Fig. 5). These results have been submitted to a statistician who has returned the following report on the fifteen-minute and three-hour intervals:

"The probability of 't' for a difference between mean is less than .02 at 15 minutes, and less than .001 at three hours. The elective cesarean section group had a significantly lower saturation at both 15 minutes and at three hours. There was no significant difference between the two groups in respect to the mean change over that period."

TABLE IV. ELECTIVE CESAREAN SECTION UNDER CONTINUOUS SPINAL ANESTHESIA

CASE NO.	TIME AFTER DELIVERY AND PER CENT OXYGEN SATURATION				
44	:15—64%				
46	:23—68%	1:23—87%	3:53—98%		
51		1:05—69%		24:00—79%	36:00—83%
52	:15—87%	1:00—90%		24:00—95%	
53	:25—69%		3:00—75%	24:00—86%	
54	:20—72%		3:00—79%	24:00—88%	
59	:15—65%	1:00—78%		24:00—91%	
58	:15—64%	1:00—77%		24:00—84%	
62	:15—51%	1:00—64%	3:00—75%	24:00—83%	
66		1:00—72%	3:00—85%	24:00—96%	
72	:15—72%	1:00—81%	3:00—87%	27:00—96%	

Comment

On the basis of these observations it appears that with the methods of analysis employed the most favorable reaction one can anticipate in obstetric spontaneous delivery is a fetal oxygen saturation of 79 per cent at 15 to 20 minutes, of 85 per cent at one hour, and of 94 per cent at three hours. These figures are dependent upon spontaneous delivery without analgesia or anesthesia and are not influenced by administration of 50 per cent nitrous oxide and oxygen during labor, or by the administration of oxygen to the newborn after delivery.

In contrast, the percentages of saturation obtained in elective cesarean section performed under low-dosage continuous spinal anesthesia lag considerably behind.

Whether this lag in oxygen saturation of moderate degree has a detrimental effect upon the central nervous system of the fetus is open to question, considering the relatively low oxygen tension at which the baby existed in utero during pregnancy.[5]

It is to be recalled, however, that these comparisons are of mean values and that certain low determinations entered into the establishment of the mean which might be productive of damage. Unfortunately, there is no test at present sufficiently sensitive to detect minor degrees of damage in the brain of the newborn.

Be that as it may, there are probably few physiologists, few pediatricians, and few obstetricians but who would prefer to see the newborn baby oxygenated at the levels described for spontaneous vaginal delivery rather than at those found after cesarean section.

In a recent analysis of the effects of Demerol and trichlorethylene on oxygen saturation of the newborn, Dr. Taylor and his associates[9] have employed the double-scale, absolute-reading, alternating-current oximeter with

an infant-sized earpiece to make continuous determinations of oxygen saturation 2 minutes to 30 minutes after delivery. A study of the oxygen saturation of arterial blood of normal newborn infants was made by the same method by Crehan, Kennedy, and Wood[10] at the Mayo Clinic. The entire problem of photoelectric determinations of arterial oxygen saturation of man was considered by Wood and Geraci[11] in 1949. In general, the results with the oximeter reveal a higher oxygen saturation at the fetal ear than is found in cutaneous blood from the fetal heel. The question might be raised as to which is the more accurate method of investigation. Consideration of this problem discloses certain advantages and disadvantages of both the microchemical and the oximeter methods.

Determinations on the fetal ear with the oximeter bring the analyzing apparatus somewhat closer to the cerebral centers than when the determination is made from the cutaneous blood of the fetal heel. The oximeter, however, requires warming of the pinna of the ear—an artificial factor—in order to accelerate capillary circulation to a state representative of arterial blood. The method is also 2½ per cent inaccurate at levels of 90 per cent oxygen saturation, and 9 per cent inaccurate at levels of 60 to 70 per cent oxygen saturation.

The microchemical methods of analysis are extremely accurate as compared with the Van Slyke determinations but it must be acknowledged that circulation is not as promptly and freely established in the heel as in the areas near the heart. In both methods capillary blood is employed for the determinations, Lundsgaard and Møller[13] having pointed out that free-flowing cutaneous (capillary) blood has essentially the same oxygen content as arterial blood.

It is probable that either method, the microchemical or the oximeter, when used consistently in a given group of cases, by a given group of investigators, presents a sufficiently accurate representation of the progressing physiologic activity of the respiratory tract and vascular tree of the newborn to be of clinical value.

Summary

1. By means of microchemical determinations of oxygen saturation of fetal capillary blood at successive intervals following delivery, it has been possible to establish figures which possibly represent the best physiologic response which may be secured in spontaneous delivery.

2. Compared with these determinations in spontaneous delivery the oxygen saturation of the fetal blood following elective cesarean section under continuous spinal anesthesia shows a definite lag.

3. It appears that this method of study may be applied to the analysis of various forms of anesthesia, technical procedure of operation, and handling of the newborn in cesarean section to lessen fetal mortality associated with this operation.

We wish to acknowledge and express appreciation to the Air-Shields Corporation of Hatboro, Pennsylvania, for their liberal support of this study, and to Mrs. June Mosenson, B.S., for technical assistance.

References

1. Potter, Edith L., and Adair, Fred L.: AM. J. OBST. & GYNEC. 45: 1054, 1943.
2. Bloxsom, A.: J. Pediat. 20: 215, 1942.
3. Eastman, Nicholson J.: Bull. Johns Hopkins Hosp. 47: 221, 1930.
4. Eastman, Nicholson J.: AM. J. OBST. & GYNEC. 31: 563, 1936.
5. Eastman, Nicholson J.: AM. J. OBST. & GYNEC. 67: 701, 1954.
6. Watts, J. Henderson, Kamp, D. H., and Davis, R. M.: AM. J. OBST. & GYNEC. 61: 1025, 1951.
7. Taylor, E. Stewart, Scott, William C., and Govan, Clifford D.: AM. J. OBST. & GYNEC. 62: 840, 1951.
8. Taylor, E. Stewart, Govan, Clifford D., and Scott, William C.: AM. J. OBST. & GYNEC. 61: 840, 1951.
9. Taylor, E. Stewart, von Fumetti, Hans H., Essig, Laurence L., Goodman, Stanley N., and Walker, Louise C.: AM. J. OBST. & GYNEC. 69: 348, 1955.
10. Crehan, E., Kennedy, R. L. J., and Wood, E. H.: Proc. Staff. Meet., Mayo Clin. 25: 2392, 1950.
11. Wood, E. H., and Geraci, J. E.: J. Lab. & Clin. Med. 34: 387, 1949.
12. Roughton, F. J. W., and Scholander, P. F.: J. Biol. Chem. 148: 541, 1943.
13. Lundsgaard, C., and Møller, E.: J. Exper. Med. 36: 559, 1922.

HYALINE MEMBRANES IN THE LUNGS OF PREMATURE INFANTS

WAYNE S. ROGERS, M.D.,* CORAL GABLES, FLA., AND PETER GRUENWALD, M.D., BROOKLYN, N. Y.

(From the Departments of Obstetrics and Gynecology and Pathology, State University of New York, College of Medicine at New York City, and Kings County Hospital)

HYALINE membranes are frequently found in the air spaces of the lungs of many premature infants and some term infants who die in the first few days of life. This pathological entity is not new; it has been described by various observers as vernix membrane, asphyxial membrane, eosinphilic membrane, congenital aspiration pneumonia, etc.[1, 2, 3, 6, 8, 12, 13, 14, 16, 23, 26] The material lining the walls of the air spaces stains red with eosin and dark gray with the Masson stain. In premature infants it is consistently associated with atelectasis. Similar membranes, not associated with atelectasis, have been observed in children and adults following a variety of diseases such as influenza, acute pneumonias, radiation pneumonitis, and rheumatic fever. The etiology, pathogenesis, and significance of hyaline membranes remain unknown, although various concepts have been suggested. Recently the problem has been studied very extensively.[4, 5, 6, 16, 18, 22] Opinion is divided as to the etiological significance of amniotic fluid on the one hand, and edema fluid on the other hand. Histochemical studies are inconclusive.[22] There is little evidence in favor of measures which have been suggested for the prevention of hyaline membrane formation.[22]

This is a study of the autopsy findings and histories of 56 newborn infants, in whose lungs hyaline membranes were present. The cases were autopsied at Kings County Hospital during the years 1947 through 1952. The infants' charts and the antenatal and hospital records of the mothers were reviewed in detail. Autopsy protocols and microscopic sections were available for all the infants. As a control for the analysis of maternal factors, one-half of the obstetrical patients in the year 1952 were chosen. Because the great majority of the infants were premature, the following comparisons were made between prematures in each group. The control group comprises 341 immature and premature infants between 400 and 2,500 grams birth weight.

Observations

Statistical analysis of the data in Table I showed no significant differences between the two groups, with regard to positive serological tests for syphilis, anemia, toxemia, twin gestation, cesarean section, breech or cephalic presentation. The Rh factor was unknown in so many of the earlier cases as to preclude any analysis. The higher incidence of forceps delivery in the control group probably is attributable to the policy prevalent on the service

*Present address: Department of Obstetrics and Gynecology, University of Miami Medical School, Coral Gables, Fla.

during 1952, when low forceps and perineotomy came to be regarded as the method of choice in the delivery of premature infants. In the previous years this policy was not definitely established. Anesthesia and analgesia do not appear to be factors as two-thirds of the babies that developed hyaline membranes were born to mothers who received neither.

In Table I, the incidence of prenatal care appears to be significantly less in the mothers of infants with hyaline membranes than in the control group.

TABLE I. COMPARISON OF MATERNAL FACTORS IN TWO GROUPS OF INFANTS, CONTROLS AND THOSE WHO DIED WITH HYALINE MEMBRANE DISEASE

MATERNAL FACTORS	CONTROL GROUP (PER CENT)	HYALINE MEMBRANE GROUP (PER CENT)
Race		
Negro	79.5	68.6
White	20.5	31.4
Prenatal care	77.0	45.1
Positive serological test for syphilis	5.3	5.4
Anemia (less than 10 Gm.)	35.8	29.7
Toxemia	19.0	9.8
Prolonged labor (30 hours or over)	0.3	4.0
Antepartum bleeding	16.7	33.3
Premature separation of the placenta	6.1	13.7
Placenta previa	0.9	13.7
Others, including marginal sinus rupture	9.7	5.9
Types of delivery		
Vertex, spontaneous	51.8	82.4
Vertex, forceps	19.0	3.9
Breech	21.1	13.7
Cesarean section	5.7	5.9
Others (version and extraction)	2.4	0.0
Twins	7.3	9.8

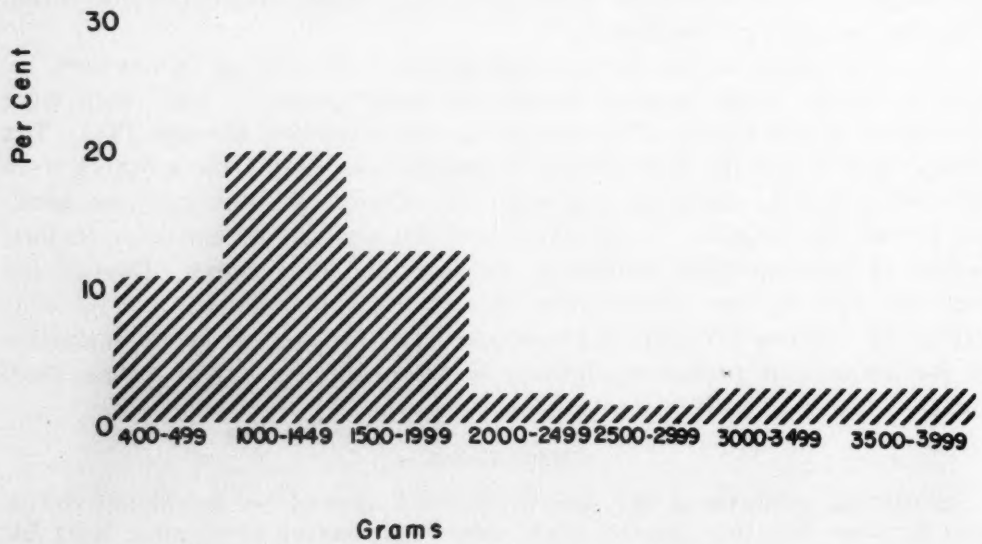


Fig. 1.—Weight relationship of 56 infants with hyaline membrane disease.

This is clarified by subdivision of the cases by birth weight. The control group is made up predominately of mothers of infants that weighed 2,000 to 2,500 grams. Such infants are less likely to have hyaline membranes and women so far advanced in pregnancy are more likely to have sought prenatal care. Comparison by infant-weight groups actually shows no significant dif-

ference between the controls and the mothers of babies with hyaline membranes, in so far as prenatal care is concerned.

One difference which does emerge is in the incidence of antepartum hemorrhage, which was significantly higher in the mothers of babies with hyaline membranes. This difference is particularly marked in cases of placenta previa but does not obtain in some other forms of hemorrhage, e.g., marginal sinus rupture.

In the study group 51 infants, or 91 per cent, were premature (weighing less than 2,500 grams at birth). There were 5 infants that weighed more than 2,500 grams and included among the latter there were 3 infants of diabetic mothers. The largest number of infants with hyaline membranes (40 per cent) were in the 1,000-1,500 gram group (Fig. 1). The majority of the infants lived between 8 and 16 hours (Fig. 2).* None of the infants died before the third hour of life. In general, the larger the infant, the longer the duration of life.

In order to ascertain when difficulty first developed, the infants' charts were studied for the first recorded appearance of symptoms related to respiratory distress (Table II). Only 10 per cent of the infants were described as being in good condition at birth or on arrival at the nursery. Fifty-two per cent of the infants had a delayed onset of respiration. Cyanosis was noted in 84 per cent before or shortly after they entered the nursery. Retraction of the thoracic cage was present in an almost equal number. Eighty-four per cent had a delayed or weak cry.

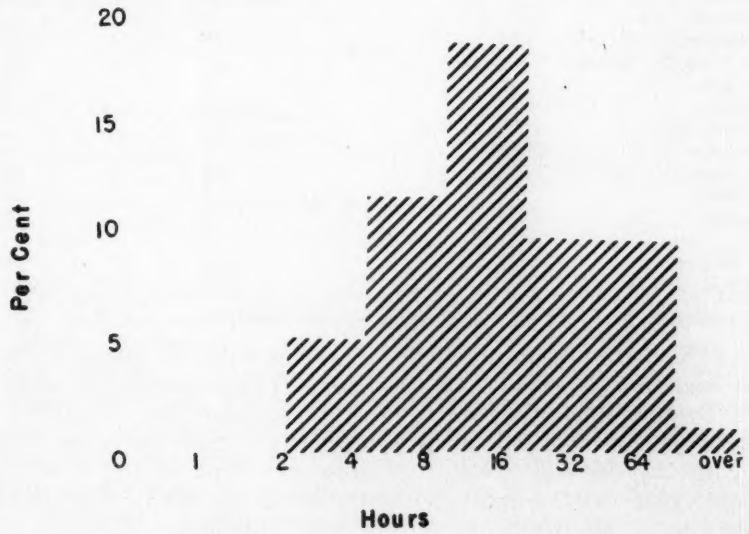


Fig. 2.—Duration of life of infants with hyaline membrane disease.

Premature infants were placed in incubators with heat and high humidity (without the use of a nebulizer) shortly after delivery. Various types of standard incubators were used. Almost all of the infants received nasopharyngeal suction and continuous oxygen. Positive-pressure oxygen was given in only one instance. Almost all the infants received either caffeine and sodium benzoate or Coramine during the time they were in distress. Symptoms cleared temporarily when the babies were first placed in the incubators, but returned shortly afterward. Only 3 infants developed fever.

*One infant with hyaline membranes not included in this series was described as stillborn but air was present in the lungs at autopsy.

Of the 5 infants whose weight was greater than 2,500 grams, 3 were born to diabetic mothers. Two of these infants weighed 2,608 and 3,020 grams, respectively. Both were delivered by cesarean section at approximately 36 weeks of gestation because of maternal acidosis. Edema of the infants was evident at birth. Weight per se therefore cannot be the sole criterion for determining the age of these babies and, judging from the clinical behavior of such infants in general, at least these 2 might be considered as premature. The third baby, that weighed 3,459 grams, was delivered spontaneously. The other 2 infants were delivered spontaneously at term. There was clinical evidence of intrauterine difficulty in one of these cases, as judged by a slow fetal heartbeat during labor. Both infants had subarachnoid hemorrhages and one also had an intraventricular hemorrhage as well as focal brain hemorrhages. Degenerative changes were present in the adrenals and liver. Petechiae were seen in the thymus, epicardium, pleura, and heart. Also, there were erosions present in the esophagus and stomach.

TABLE II. FETAL ASPECTS* OF INFANTS THAT DIED WITH HYALINE MEMBRANE DISEASE

FETAL ASPECTS	NO.	PER CENT
Condition at Birth or on Arrival in Nursery.—		
Poor	25	50
Fair	15	30
Good	5	10
No comment	5	10
History of First Breath.—		
Delayed	26	52
Immediate	18	36
No comment	6	12
Onset of Cyanosis.—		
Present immediately after birth	26	52
Noted in nursery (approx. 1-4 hours)	16	32
Later in life	4	8
No comment	4	8
Onset of Retractions.—		
Present immediately after birth	18	36
Noted in nursery (approx. 1-4 hours)	23	46
Later in life	8	16
No comment	1	2
Cry.—		
Delayed or weak	44	88
Immediate or strong	6	12

*Based on 50 infants, as 6 extramural deliveries were excluded.

Forty-two per cent of the mothers in our series were admitted to the hospital because of some complication of pregnancy. This is consistent with what has been noted by other investigators.[4, 6, 12, 24] Antepartum bleeding, especially that related to placenta previa, was increased significantly as compared to its incidence in the control group. Sixteen per cent of the controls had antepartum hemorrhage with a fetal mortality of 52 per cent. The fetal mortality was 20 per cent in cases with no antepartum bleeding.

Potter[20] and Blystad[4] have noted that a significant percentage of infants with hyaline membranes had been delivered by cesarean section, and also have emphasized that some of the term infants in their series were so delivered. There were 5 cesarean sections in our series; all 5 infants were premature. Two of these sections were for maternal diabetes. One was done at twenty-eight weeks of gestation with delivery of a 1,550 gram infant in a patient with epidermoid carcinoma of the cervix. One was done because of chronic hypertension and superimposed toxemia. The infant weighed 1,559 grams. The fifth was an elective repeat cesarean section with delivery of a 1,960 gram infant. Chapple[22] has suggested that high levels of progesterone may cause the accumulation and impede absorption of fluid in these infants' lungs. During pregnancy pregnanediol excretion increases until the ninth

month. Prior to the onset of labor and after delivery, the excretion falls rapidly.[7] In delivery by cesarean section, before the onset of labor, this does not occur.

There were 5 twin gestations, all of which terminated prematurely. In only one instance were hyaline membranes found in both infants and in these particular cases the membranes were scattered and scanty. In the remaining pairs the lesion was present only in the infant delivered first, regardless of variations in weight. One of the infants, delivered as a second twin, survived after a stormy hospital course clinically described as pneumonia and may have had nonfatal hyaline membranes. This infant weighed 1,701 grams and was the largest member of the entire group. The remaining 3 twins with hyaline membranes had atelectasis at autopsy.

The incidence of several pathological findings in this series (Table III) was compared with that in a larger series of unselected infants.[11] There were no significant differences between the two series in the incidence of pneumonia, petechiae in the thoracic viscera, focal hemorrhages or necrosis in the adrenal cortex, or focal hemorrhage in the brain.

TABLE III. ASSOCIATED PATHOLOGICAL LESIONS IN INFANTS WITH HYALINE MEMBRANE DISEASE

LESIONS	NUMBER	PER CENT
Pneumonia	14	25.0
Degenerative changes in liver	17	30.0
Degenerative changes in adrenals	11	19.7
Erosions of stomach or esophagus	22	39.3
Petechiae (thymus, epicardium, pleura, esophagus)	46	82.1
Dilatation of heart	8	14.3
Brain lesions	26	46.5
Subarachnoid hemorrhage alone	3	5.4
Intraventricular hemorrhage alone	3	5.4
Subdural hemorrhage	3	5.4
Tears of tentorium or falx	2	3.6
Subarachnoid and intraventricular hemorrhage	7	12.5
Petechial hemorrhages	14	25.0

Pathologically there is a difference between the hyaline membranes of premature infants and those of infants born at term. The former are found in respiratory bronchioles and alveolar ducts, while the alveoli proper are completely collapsed. These membranes do not contain the characteristic constituents of vernix caseosa, such as cornified cells and large amounts of fatty material. In term infants with hyaline membranes these substances are contained in the alveoli as well as the bronchioles; many alveoli are expanded with fluid and vernix in various degrees, and the uniform atelectasis of prematures is absent. In the present cases, these differences between the premature and mature infants were consistently found. Examination of the microscopic sections, performed without knowledge of the weights, showed characteristic features as just described for infants born at term, in the 2 term infants of nondiabetic mothers. Intermediate conditions with the absence of characteristic atelectasis of prematures, and without evidence of vernix material, were seen in 2 of the babies of diabetic mothers and in 2 infants that weighed 1,600 and 2,400 grams, respectively. All the others had the characteristic findings as described for premature infants.

Comment

In the main, the present-day controversy concerns the pathogenesis of hyaline membranes and their physiological significance. There may have been

a tendency to focus most of the attention upon this microscopic finding and to regard lightly many of the other aspects. There may be other accompanying conditions and findings in these babies which are in turn closely associated with each other, namely, hypoxia, atelectasis, vascular congestion and injury, shock and pulmonary edema. The formation of a hyaline membrane may be a result of these conditions and not the primary cause of death.

As is borne out in this paper and in other reports[4, 6, 12, 24] the incidence of antepartum bleeding is increased significantly in this group; it probably contributes to the degree of hypoxia. As shown in our control group, it appears that antepartum bleeding is hazardous for prematures generally. The occurrence of fetal hypoxia caused by hemodynamic changes in the placentas of such patients has been postulated.[19] Clifford[22] studied a selected group of infants delivered prematurely because of maternal bleeding due to placenta previa. At the time of autopsy all the infants had hyaline membranes in addition to congestion and edema. Other evidence of hypoxia such as petechiae was also found.

A shocklike state may be present in the infants. Pathological findings such as degenerative changes in the adrenals, petechiae, dilatation of the heart, gastroinestinal erosions, and pulmonary edema would seem to bear this out.[10] Capillary fragility and injury and vascular congestion are prone to occur, especially in hypoxic or shock states.

Let us examine the clinical and experimental evidence at hand. Hyaline membranes occur in older children and in adults who have died of influenza, rheumatic fever, acute pneumonias, and radiation pneumonitis. Other common findings in these cases are pulmonary edema and pulmonary capillary damage. Hyaline membranes have been produced in experimental animals by various investigators. One approach was the use of intratracheal injections of a variety of materials.[4, 9, 13] Others have found these methods unsuccessful.[6, 17] Atelectasis usually associated with human hyaline membranes in premature infants could not be produced. Vascular injury may be the important factor in these cases. Miller and his co-workers[19] produced a similar lesion in rabbits by bilateral vagotomy. Pulmonary edema was striking in these laboratory animals. Bruns and Shields[5] were able to produce hyaline membranes in adult guinea pigs with high concentrations of oxygen. Histological examination of these guinea pig lungs also showed shedding of the epithelial structures and the presence of edema fluid. In the present cases, the membranes were found over areas equally devoid of epithelium.

How these membranes are formed is still unknown, but it appears that edema fluid rather than aspirated vernix is the more likely cause. Whatever the etiology, hyaline membranes are produced only after air breathing for at least one hour. Amniotic fluid is quickly absorbed and the lung can handle large quantities. If for some reason this fluid were not absorbed, all of the infants would be in a great deal of difficulty from the beginning. Some infants with hyaline membrane disease live for forty-eight to seventy-two hours and it is doubtful whether amniotic fluid could be present throughout this period of time.

As was previously mentioned, hyaline membranes in premature infants are characteristically associated with a peculiar type of atelectasis. This same form of atelectasis also occurs without hyaline membranes, but with the same grave consequences. It has therefore been suggested[21, 22] that the significant lesion is this characteristic atelectasis of prematures, and that this may or may not be associated with the presence of hyaline membranes. No systematic studies of prematures with atelectasis alone are available.

Conclusions

1. In a series of 56 infants who at autopsy showed pulmonary hyaline membranes, various factors in the mothers and offspring have been reviewed. Among these, prematurity and maternal antepartum bleeding appear to be clinically significant.

2. It is important to distinguish the frequently occurring atelectasis with hyaline membranes of premature infants from vernix membranes of infants born at term. In prematures a peculiar type of atelectasis of the alveoli occurs in association with dilatation of the terminal air passages. The latter may or may not be lined by hyaline membranes. This type of atelectasis appears to be favored by some unknown factor associated with prematurity. It is probable that this entity is more significant than the hyaline membranes which are inconstantly associated with it.

3. Hypoxia, shock, vascular injury, and pulmonary edema are probably important factors contributing to the death of these infants, either by enhancing their pulmonary lesions or by other effects.

References

1. Arey, J. B.: New Orleans M. & S. J. **100**: 258, 1947.
2. Arey, J. B.: J. Pediat. **34**: 44, 1949.
3. Benner, M. C.: Arch. Path. **29**: 455, 1940.
4. Blystad, W., Landing, B. H., and Smith, C. A.: Pediatrics **8**: 5, 1951.
5. Bruns, P. D., and Shields, L. V.: Am. J. Obst. & Gynec. **61**: 935, 1951.
6. Dick, F., Jr., and Pund, E. R.: Arch. Path. **47**: 307, 1949.
7. Dieckmann, W. J.: The Toxemias of Pregnancy, ed. 2, St. Louis, 1952, The C. V. Mosby Company.
8. Farber, S., and Sweet, L. K.: Am. J. Dis. Child. **42**: 1372, 1931.
9. Farber, S., and Wilson, J. L.: Arch. Path. **14**: 450, 1932.
10. Gruenwald, Peter: Arch. Pediat. **67**: 103, 1952.
11. Gruenwald, Peter: To be published.
12. Helwig, F. C.: Am. J. Obst. & Gynec. **26**: 849, 1933.
13. Johnson, W. C., and Meyer, J. R.: Am. J. Obst. & Gynec. **9**: 151, 1925.
14. MacGregor, A. R.: Arch. Dis. Childhood **14**: 323, 1949.
15. MacMahon, H. E.: Am. J. Path. **24**: 919, 1948.
16. Miller, H. C., and Hamilton, T. R.: Pediatrics **3**: 735, 1949.
17. Miller, H. C., Hamilton, T. R., Wise, G. W., and Wenner, H. A.: Am. J. Path. **25**: 253, 1949.
18. Miller, H. C., and Jennison, M. H.: Pediatrics **5**: 7, 1950.
19. Miller, H. C., Behrl, F. C., and Gibson, D. M.: Pediatrics **7**: 611, 1951.
20. Potter, E. L.: Pathology of the Fetus and the Newborn, Chicago, 1952, The Year Book Publishers, Inc.
21. Ranström, S.: Acta paediat. **42**: 323, 1953.
22. Report of the Fifth M. & R. Pediatric Research Conference at St. Christopher's Hospital for Children, Philadelphia, April, 1952.
23. Rosenthal, M.: J. Pediat. **6**: 71, 1935.
24. Russ, J. D., and Strong, R. A.: Am. J. Obst. & Gynec. **51**: 643, 1946.
25. Tran-Dinh-De and Anderson, G. W.: Obst. & Gynec. Surv. **8**: 1, 1953.
26. Tregillus, J.: J. Obst. & Gynaec. Brit. Emp. **58**: 406, 1951.

VASCULAR ANOMALIES OF MOUSE FETUSES EXPOSED TO ANOXIA DURING PREGNANCY*

C. G. TEDESCHI, M.D., AND THEODORE H. INGALLS, M.D., BOSTON, MASS.

(From the Department of Epidemiology, Harvard University School of Public Health)

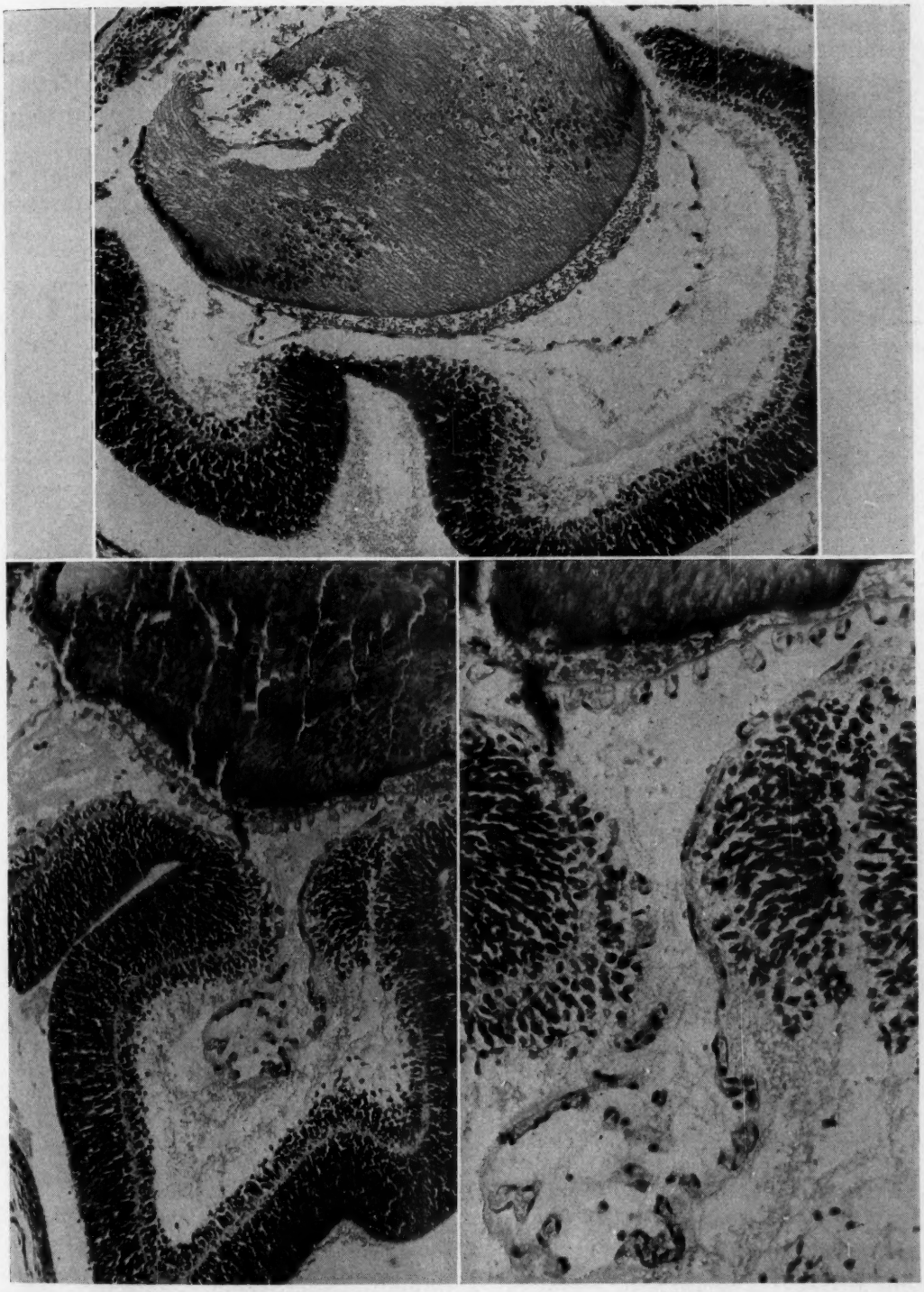
ACQUIRED congenital defects of the eye previously described[1] appeared to have their basis in disorders of vascularity; they were induced in the offspring of mice subjected to low atmospheric pressures in the latter part of pregnancy. The environmental insult (fetal hypoxia) interrupted orderly growth of the angioblastic tissue and permanent sequelae occurred, depending on the timing, degree, location, and duration of the anoxic stress.[2, 3] Additional vascular defects were found in the skin, subcutaneous tissue, and central nervous system and were characterized by abnormalities of distribution, quantity and quality. The anomalous formations were of microscopic dimensions but otherwise conformed to the description of hamartomatous growths by Albrecht[4] 50 years ago.

Classification of such vascular defects is customarily according to whether they are telangiectatic or angiomatous in nature. Simple telangiectasia, the dilation of a blood channel out of proportion to physiologic need, is thought to have its basis in structural (qualitative) deficiency of the vessel wall. Plexiform angioma represents a defect in distribution—the crowding of unevenly spaced blood channels into an area, the vascular units being separated from each other by the tissues of that area. Angioma simplex is a quantitative disorder resulting from an excessive proliferation of blood channels, within vasoformative mesenchyma, in a well-circumscribed area. The existence of borderline defects and combinations of defect indicate that these categories are oversimplified. As with other congenital anomalies a gradient is to be encountered with extremes merging into each other through a series of intergrade conditions. The principle is illustrated by the cavernous type of angioma which has the properities of a combined defect—quantitatively excessive proliferations of blood channels and qualitative deficiency of vessel walls resulting in patulous dilation of the channels.

The various hereditary and environmental factors which cause the primordial blood capillaries to sprout off in normal patterns from the primitive vascular system and what factors determine whether capillaries become arteries or veins are not completely understood, but adaptability is indicated by the observations of Sabin[5] in chick and pig embryos. She showed that a vessel could serve first as an artery, then be reduced to a capillary plexus and subsequently develop into a vein or receive arterial connections and become an

*Aided by grants from United Cerebral Palsy, the American Heart Association, and the Association for the Aid of Crippled Children.

A.



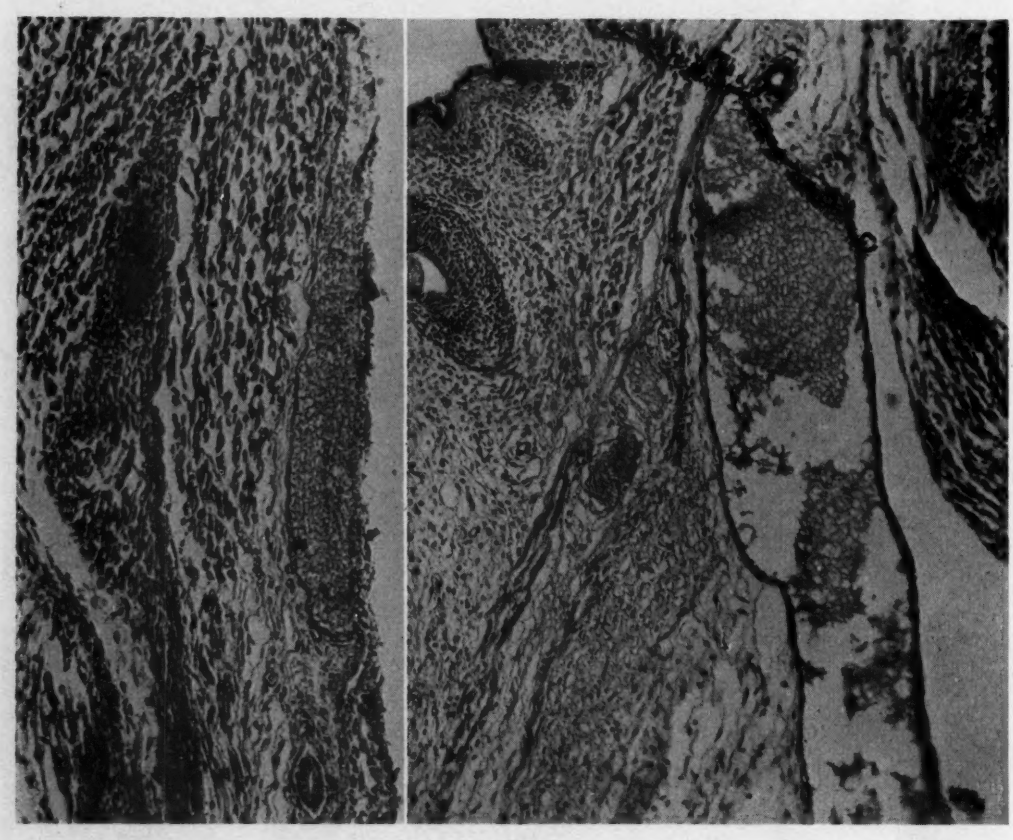
B. *C.*

Fig. 1.—*A*, Normal eye (top) and unilateral defects of the other eye (bottom) in a fetus subjected to intrauterine hypoxia on the sixteenth day of pregnancy. The ocular defect clearly involves the lens and retina (folding) and involves abnormal vascularity of the vitreous. (Hematoxylin and eosin. ×200; reduced ⅓.)

B, Abnormal eye showing retinal folding and increased vascularity within the fold. (×200; reduced ⅓.)

C, A higher magnification of vascularity details. (×400; reduced ⅓.)

arterial plexus. Clark and Clark[6] have shown that the advance of budding capillaries is affected by the condition of the substrate into which they are growing; and that mechanical, thermal, or chemical stimuli may induce the formation of new capillary sprouts with subsequent remodeling of already vascularized areas; the process under these circumstances is essentially reparative. The retention of sprouting endothelial channels as blood capillaries, their disappearance or subsequent development as arteries or veins are further determined by two main hydrodynamic factors according to Thoma[7]: pres-



A. *B.*

Fig. 2.—*A*, Subepidermic telangiestasia in a fetus subjected to hypoxic stress on the fourteenth day of conceptual age.

B, Intradermic telangiectasia in a fetus with extensive cutaneous hemorrhage submitted to anoxic insult on the seventh day of gestation. Cutaneous hemorrhages were prominent findings in both animals. (×200; reduced ⅓.)

sure and volume of blood flow, pressure regulating the thickness of the wall and flow the size of the lumen. Newly formed capillaries are particularly susceptible to environmental changes; they may become widened to a diameter three or four times the usual capillary size and rupture upon slight external pressure or increased blood flow, with resulting extravasation of red cells and plasma into the surrounding tissue.

Information on the physiologic effects of oxygen supply on the development of the vascular system has been contributed by the observations of Campbell[8] on the retinal vessels of newborn rats placed in normal and low pressure

environment. His results indicate that oxygen tension in the tissues around the vascular bed exerts a significant influence on developing vessels. He observed that retinal blood vessels grew toward the areas of low oxygen tension and ceased to extend when areas of higher oxygen tension were reached. He described capillaries arising from venous loops of the arteriovenous arcades in a pattern determined, so he inferred, by tissue oxygen tensions—and these in turn were determined by proximity to arterioles as compared with venules.

Fig. 3.—Irregularly distributed blood channels crowded together in the forebrain of a fetus that received anoxic stress on the fifteenth day of gestation. The blood channels are separated one from the other by poorly differentiated neural elements, the whole resulting in a pattern of a plexiform of angioma. (×400; reduced ¼.)

The acute sequences resulting from critical anoxia have been described by many. The first change to be observed is intense congestion, involving all organs and tissues and extending to the finest capillaries. This is followed by liberation of edema fluid into the tissue spaces and the body cavities and by extravasation of red cells, either through diapedesis or actual rupture of small vessels.[9] Structural and functional consequences for the nervous system have been described by Windle[10] but persisting effects of anoxia leading to formation of vascular hamartomas in rodents have not, to our knowledge, been demonstrated.

The present study examines the microscopic nature of vascular defects induced in rodents by prenatal anoxia. The observations made are of a qualitative rather than a quantitative nature for the growth of the vascular system is a relatively dynamic and continuous process throughout gestation—unlike final differentiation of such tissues as the palate, for example, which closes but once; or the ribs which appear but once.

Material and Methods

The pregnant females producing these fetuses had been submitted to reduced atmospheric pressure simulating altitudes of 25,000 or 28,000 feet (260 or 280 mm. of mercury) as previously described.[3] Living fetuses were first examined for gross malformations such as kinky tail, cleft palate, cranioschisis, and open eye. Subsequently the head was severed, decalcified, and embedded in paraffin, whereas the trunk was cleared and examined for osseous malformations; thus only the head was subjected to microscopic study.

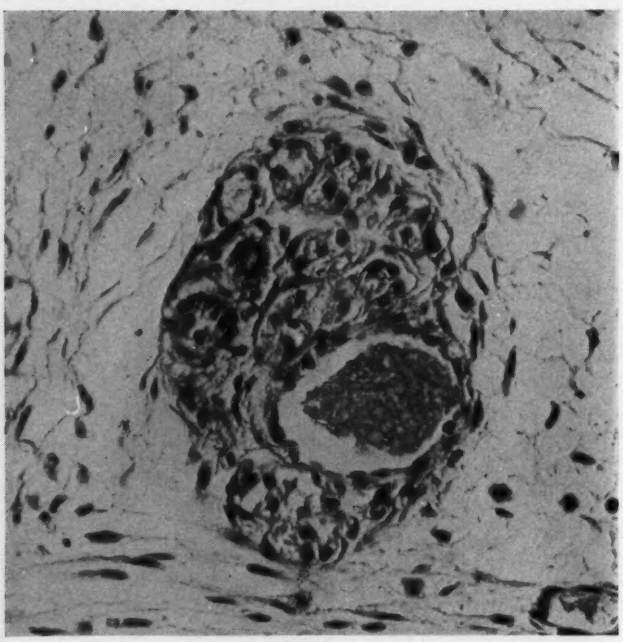


Fig. 4.—Intradermic conglomerate of thin-walled blood channels about a thrombosed blood vessel in a fetus submitted to intrauterine hypoxia on the seventh day of gestation. The formation is interpreted as a quantitative disorder—angioma simplex. (×600; reduced ¼.)

Serial coronal or tangential sections about 6 microns thick and stained with hematoxylin and eosin were studied. Of 53 fetuses 27 manifested signs of vascular disorders. Three of these also had cleft palate; 8 had ocular defects, and intracutaneous hemorrhage was a prominent feature in 10 animals. Vascular defects were evaluated by comparison with vascular structures of corresponding regions of 23 control embryos of similar conceptual ages. All fetuses were delivered prematurely by section on the nineteenth day of gestation.

Results

Vascular patterns were judged abnormal in the fetuses being studied after test animals were compared with control animals in respect to distribution, quantity, or quality of vascular elements. Fig. 1 illustrates such

comparison in the same animal which had one normal and one congenitally defective eye. Fig. 2 shows a single telangiectatic blood channel, observed in the scalp of two different mouse fetuses. Irregularities in thickness of the vessel walls, variations from tract to tract in the staining properties of the collagen, and loss of alignment of endothelial cells are interpreted as indications of an inherent structural deficiency of the vessel walls.

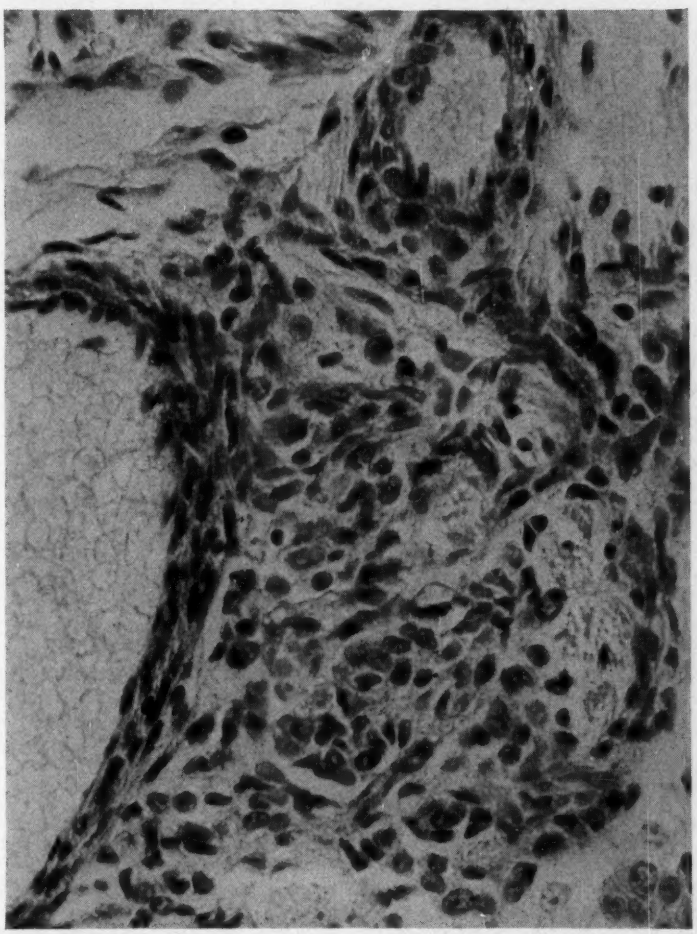


Fig. 5.—Same type of vascular disorder illustrated by Fig. 4, showing transitional patterns from undifferentiated mesenchymal cells to endothelial cells with blood channels. The lesion was found in the palatine area of an animal with cleft palate. Hypoxia on the fifteenth day of gestation. (×800; reduced ¼.)

Excessively numerous blood channels in one area of the forebrain are shown by Fig. 3. There were concurrent disorders in neuronal architecture with condensation of cells in some areas, rarefaction and poor cellular differentiation in others. The vascular anomaly is characterized by crowding of thin-walled, normal-sized channels into a circumscribed area, with interposition of nervous tissue elements between vascular units. Morphologically, the basic defect is a disorder in distribution rather than in the kind of blood capillaries. Two comparable vascular disorders of the scalp were present in the same animal.

Excessive proliferation of blood capillaries, grouped together in a limited area and with interposition of no other tissue than a variable amount of vasoformative fibrocellular stroma is illustrated by Fig. 4, showing an intra-

dermic conglomerate of thin-walled blood channels, in proximity to a large thrombosed blood vessel. There were no communications apparent between channels and each vessel showed a well-defined wall of homogeneous thickness, a finding which is consistent with independent circulation.

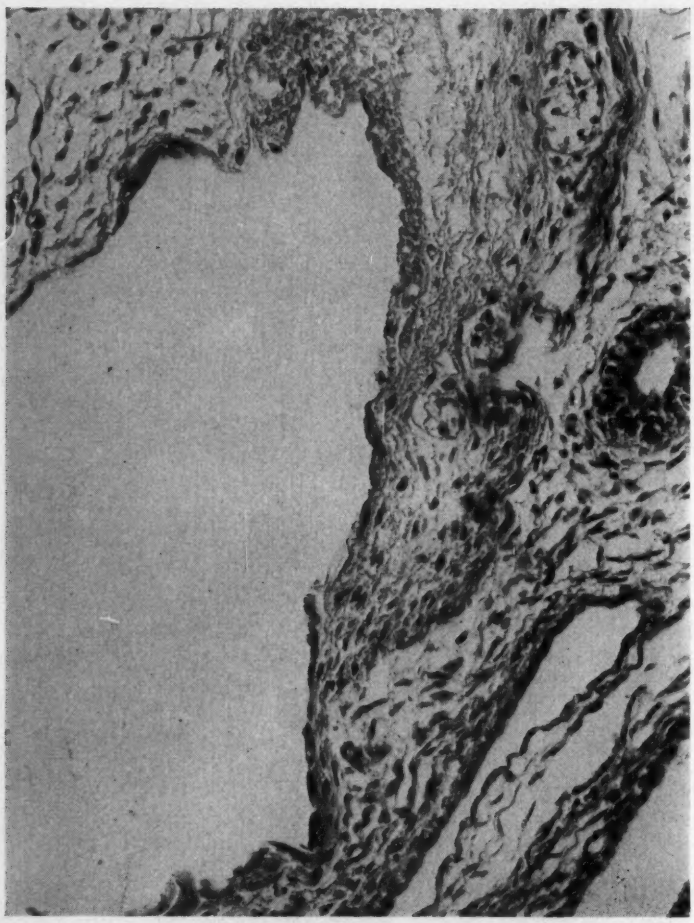


Fig. 6.—Telangiectatic intradermic blood channel showing a broad tract of the wall deprived of endothelial lining and escape of red cells in the surrounding tissue. From a fetus that received hypoxic stress on the fifteenth day of gestation, and displayed multiple cutaneous vascular disorders and hemorrhages. (×400; reduced ¼.)

An earlier manifestation of a similar type of anomaly is illustrated by Fig. 5; this shows transitional patterns from undifferentiated mesenchymal cells to endothelial cells with formation of poorly differentiated blood channels within the palatine area of an animal with cleft palate. The association suggests that the genesis of the capillary defects, like that of the palatine anomaly, resided in the original hypoxic insult; quantitative data are not available to prove the supposition, however. The hypothesis can be tested by experiments suitably designed to study the development of both kinds of defects in a series of animals sacrificed at regular intervals after exposure to hypoxia. It is more important to establish the principle involved than the specific association of vascular defects with cleft palate. Hence the ribs and vertebra should prove more profitable sites to examine for pathological sequences, there are so many more "target sites" that could register the basic disturbance.

In addition to the vascular anomalies that have been described, other, more conventional forms of injury were encountered. Damage to endothelium was shown by cells that were swollen or distorted in alignment or with the cellular outlines poorly made out or absent. Some of these changes are shown by Fig. 6, displaying partial absence of endothelial lining in a telangiectatic intradermal blood channel and escaped red cells just outside the injured wall.

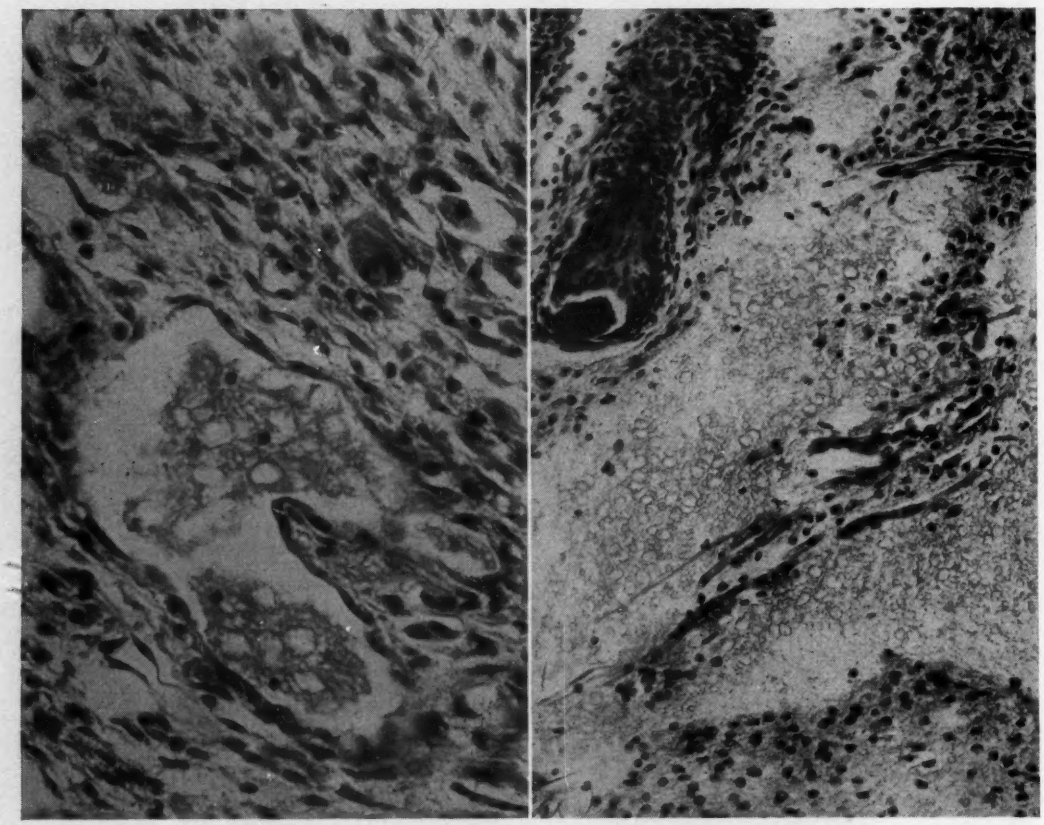
Fig. 7.—Thrombosed blood channels in the dermis of a fetus submitted to intrauterine anoxia on the seventh day of gestation. There is marked perivascular edema. (×400; reduced ¼.)

Agglutination of red corpuscles and vascular occlusion were frequently seen in association with endothelial damage (Fig. 7); both blood capillaries and small arteries and veins were seen to be involved. Endothelial damage did not seem to be the only factor operating in the formation of the thrombi, because they were noticed also in channels lined by normal-appearing endothelium. The thrombi were composed of agglutinated red cells which showed various degrees of disintegration (Fig. 8). Fibroblasts were seen at times to invade the thrombotic masses, a pattern that was interpreted as indicating early organization.

Vascular congestion, extending to the finest capillaries, hemorrhage, and tissue edema were frequently associated findings. At times the extravasations of red cells and plasma were small; at other times they were ex-

tensive. At the edges of the extravasations, the mesenchymal cells were increased in number, including macrophages and bizarre-shaped giant cells containing cellular debris (Fig. 9).

Lymphangiectasia also was occasionally observed. Fig. 10 shows both dilatation of normal-appearing lymph channels (simple lymphangiectasia) and dilatation of spaces with endothelial septa and intraluminal buds of endothelial cells (cavernous lymphangioma) in the dermis of the same fetus; the mother had been subjected to hypoxia on the thirteenth day of gestation.



A. *B.*

Fig. 8.—*A*, Agglutination of partially hemolyzed corpuscles in the lumen of a blood channel distorted by a thick spur of cellular mesenchyma. A giant cell with bizarre-shaped nucleus is noticeable a short distance from the vessel wall. Multiple cutaneous hemorrhages were observed in the skin of the fetus which had been subjected to intrauterine anoxia on the fifteenth day of conceptual age. (×800; reduced ⅓.)

B, Extravasation of red cells and plasma in the dermis of the same animal. (×400; reduced ⅓.)

Comment

It is well known that when the oxygen tension in the blood falls below a critical level, the vessels dilate; and if the hypoxia is severe necrosis and rupture of the renal wall ensue. Tissue cells necessarily share in the consequences and various degrees of transudation, hemorrhage, and tissue damage follow. Damage of blood channels is next followed by sprouting of new capillaries[11] and doubtless the sequences that occurred in the fetuses studied were intrauterine anoxia, vascular damage, endothelial proliferation, and formation of new channels. Biochemical sequences are not ignored; they

simply are not known. The ultimate effects on vascular structures were hamartomatous in nature. The permanent effects on differentiation of certain cartilagenous, osseous, and ocular structures have previously been demonstrated.

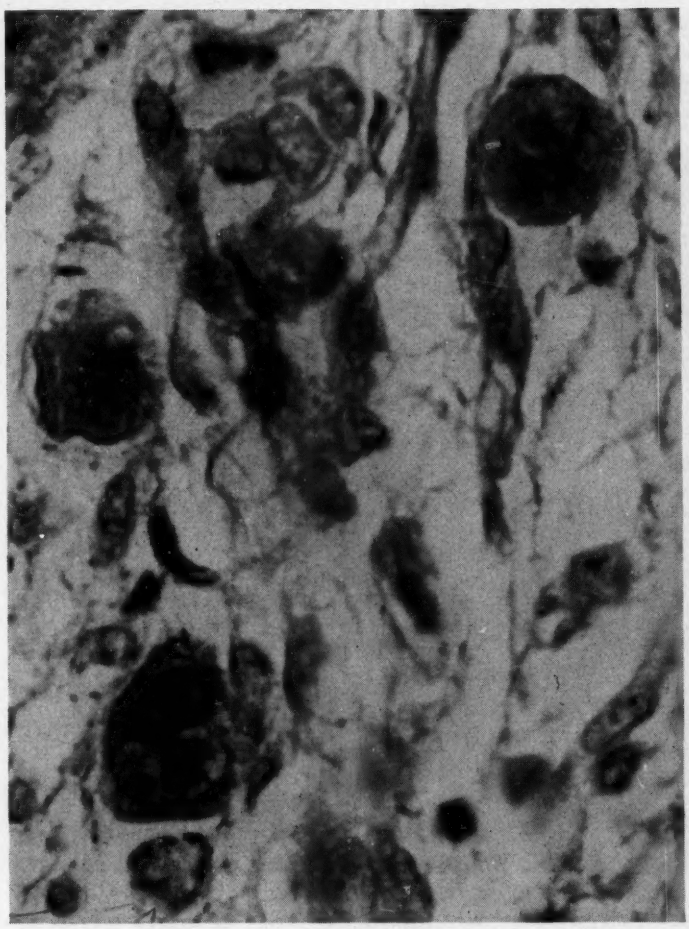
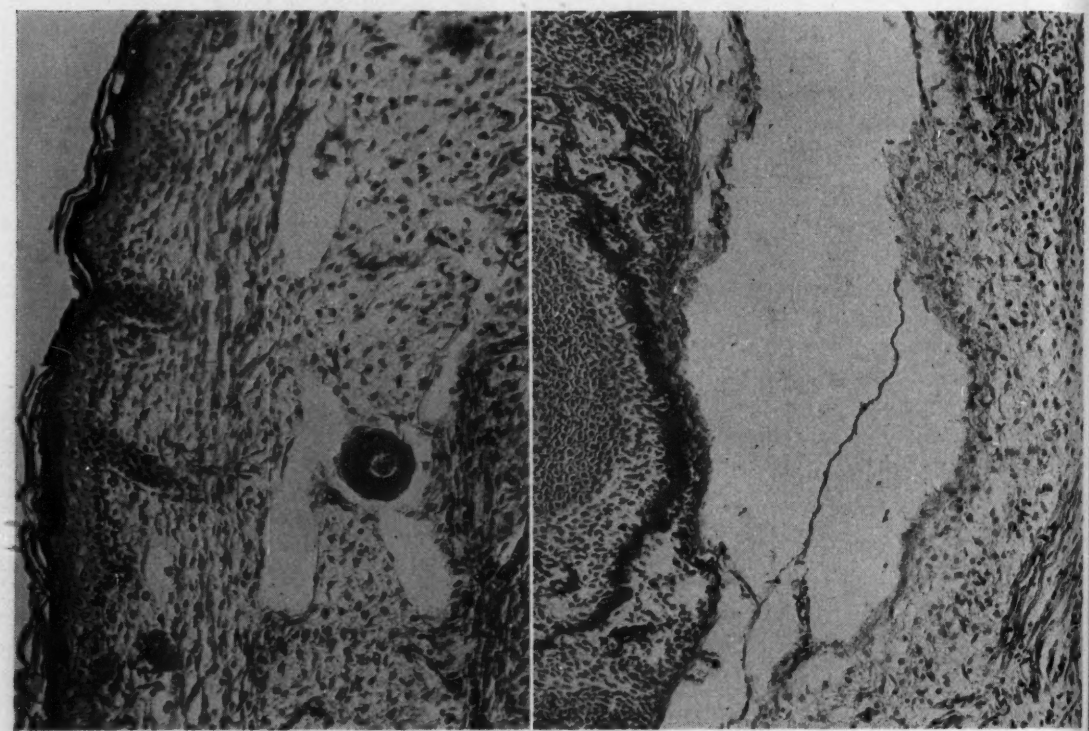


Fig. 9.—Mesenchymal cell reaction including giant cells with bizarre-shaped nuclei in the dermis of a fetus with extensive hemorrhage and edema after intrauterine anoxia on the thirteenth day of gestation. (×1600, reduced ¼.)

Deviations from normal patterns of blood vessel formation were observed to occur without relation to the stage of development reached by the embryo at the time of intrauterine stress. A stage-specific defect is hardly to be expected in the vascular system. If vascular growth is conceived of as the addition of arcades of capillaries upon arcades of previously formed vessels (like the arches of a Roman viaduct) then vascular injury can be sharply localized in time but without sufficient telltale morphologic evidence being left behind to date the injury, as often happens with deformities of the bones or eyes or teeth. No doubt the location of anoxic injuries in relation to blood and lymph channels and soft tissues in general would vary as gestation progressed, but special three-dimensional studies would be necessary to demonstrate such variations quantitatively. For example, the number of hamartomatous processes that were found at a specific location after anoxia on any

given day could be counted in test animals and compared with those found in controls. Such counts were not made and the facts presented here thus take on a qualitative rather than quantitative significance.

The nature of the vascular anomalies demonstrated and the probable mechanism of pathogenesis may have application to the genesis of hamartomatous formations in human beings. Supporting an interpretation that human hemangiomas are usually of congenital origin is the fact presented in Watson and McCarthy's[12] review of 1,001 cases of vascular tumors, that 73 per cent of their patients presented evidence of the disorder at birth.



A. *B.*

Fig. 10.—*A*, Intradermic lymphangiectasia in a fetus submitted to intrauterine anoxia on the thirteenth day of gestation. (×400; reduced ⅓.)

B, Dilated lymph channels and intraluminal endothelial septa giving rise to a pattern like that of a cavernous lymphangioma. From the same fetus. (×200; reduced ⅓.)

In more than 85 per cent of their cases the lesion had developed before the end of the first year; in others it was probably present at birth, but small or unnoticed. It is well known that hemangiomas may continue to increase in size after birth; a "vicious circle" may operate in determining this extension of the process. The observation of Hess, Mohr, and Bartelme[13] that hemangiomas of the skin are more frequent among prematurely born infants than in full-term siblings should be extended to a concern with etiology. The indications are that clarification of the pathogenesis and epidemiology of birthmarks will aid clarification and partial control of congenital deformities. Our observations further the conception that, while mechanical factors are important in determining the course of the angiomas, their origin and extension often depend on anoxic disturbances of the vascular system. A lack of oxygenation for three minutes, according to Landis,[14] is sufficient

to increase by four times the normal permeability of the capillary wall. It has been estimated that the critical blood oxygen content required to produce an increase in capillary permeability lies below approximately 4 to 6 volumes per cent or 20 per cent oxyhemoglobin saturation.[15] But even at hypoxemic levels, well within a range compatible with life and in the absence of general permeability changes, localized injuries, vascular rupture, and hemodynamic sequences take place which have far-reaching effects.

It is to be recalled that the embryo lives under conditions of reduced oxygen tension, normally compensated for by a high hemoglobin content of the blood and a fuller utilization of available oxygen in the tissues. Despite these compensatory mechanisms, it is known that the integrity of the embryo, like that of the infant and adult, is dependent on a continuous and adequate supply of oxygen and that large reductions for a few hours or even smaller reductions if they last for days may result in permanent anoxic damage; partial proof is advanced in the observations recorded here.

Application of this work to hamartomatous growths of human beings is necessarily poorly defined; and yet there has been much speculation along similar lines. Thus Tedeschi sought some systemic link between the superficial vascular anomalies of the Lindau-von Hippel syndrome and the frequently associated visceral defects.[16] Similarly, mental retardation, cerebral angiomatosis, and nevus flammeus of the face need an integrated explanation as isolated parts of the Sturge-Weber syndrome; and the association of phlebectasia and dyschondroplasia[17] is too frequent not to have significance. Abnormal vascularity is a prominent feature of Mongolism[2] and of the neural defect of anencephaly.[18, 19] Likewise, the frequent association of "berry" aneurysms of the circle of Willis with congenital polycystic kidney[20] and abnormal development of meningeal vessels in association with cardiac abnormalities in newborn infants[21] need explanation in systemic terms; many anatomically unrelated defects unquestionably have a common pathogenesis in vascular disease.

The microscopic problem of the genesis of congenital vascular defects is held to be basic to an understanding of gross congenital anomalies in general. Even the fundamental challenge of classification of gross anomalies presents striking similarities with the attempts that have been made to classify vascular defects microscopically. Thus, from the time of the first attempts to approach congenital deformities scientifically, the nosologic challenge was to explain only three kinds of defects: anomalies (monstra) "per excessum" (teratomas, tumors, excrescences), "per defectum" (missing and dwarfed tissues), and "double monsters." It is no accident that classification of hamartomatous defects involves judgments concerning quantity, quality, and distribution of basic elements—and that defects cannot be simply and sharply assigned to one morphologic etiological category. It is inferred that the gross structural defects described previously had their genesis in vascular disorders induced by hypoxia at the site or even at some distance from the defect. This hypothesis can be tested by appropriately designed experiments.

Summary and Conclusions

Microscopic study of mouse fetuses indicates that intrauterine anoxia of five hours' duration can cause disorderly development of fetal blood vessels. A gradient-like variety of vascular patterns is to be observed, with the basic abnormality one of distribution, quantity, or quality of the endothelial or supporting elements. Such congenital vascular defects were seen in the skin, in the subcutaneous tissue, in the eye, and in the central nervous

system, as a gradient corresponding with hamartomatous processes seen in human beings such as vascular nevi, telangiectasia, capillary or plexiform angiomas; lymphangiectasia and cavernous lymphangioma.

These hamartomatous defects occurred in association with gross congenital anomalies that have been reported previously: cranioschisis, hemivertebra and rib defects, kinky tail, cleft palate, and variations of open eye and micropthalmia. They did not appear to be "stage specific" as did the gross anomalies of highly differentiated tissues. It is inferred that they are permanent vascular "scars" of the systemic insult previously delivered; and that the acute changes of the vasoformative mesenchyme contribute to and underlie the gross anomalies and have a common pathogenesis with them. These observations add further evidence to the conception that vascular disorders and circulatory disturbances during development can cause anatomically unrelated defects.

References

1. Ingalls, T. H., Tedeschi, C. G., and Helpern, M. D.: Am. J. Ophth. **35**: 311, 1952.
2. Ingalls, T. H.: New England J. Med. **243**: 67, 1950.
3. Ingalls, T. H., Curley, F. J., and Prindle, R. A.: Am. J. Dis. Child. **80**: 34, 1950.
4. Albrecht, E.: Verhandl. Deutsch. path. Gesellsch. **70**: 153, 1904.
5. Sabin, F. R.: Contrib. Embryol. **9**: 213, 1920.
6. Clark, E. R., and Clark, E. L.: Am. J. Anat. **66**: 1, 1940.
7. Thoma, R.: Textbook of General Pathology and Pathological Anatomy, translated by Bruce, London, 1896.
8. Campbell, F. W.: Tr. Ophth. Soc. U. Kingdom (1951) **71**: 287, 1952.
9. Clifford, S. H.: Am. J. Obst. & Gynec. **39**: 388, 1940.
10. Windle, W. F.: Asphyxia Neonatorum. Its Relation to the Fetal Blood, Circulation and Respiration and Its Effects Upon the Brain, Springfield, Ill., 1950, Charles C Thomas, Publisher.
11. Abell, R. G., and Schenck, H. P.: J. Immunol. **34**: 195, 1938.
12. Watson, W. L., and McCarthy, W. D.: Surg., Gynec. & Obst. **70**: 569, 1940.
13. Hess, J. H., Mohr, G. J., and Bartelme, P. F.: The Physical and Mental Growth of Prematurely Born Children, Chicago, 1934, University of Chicago Press, p. 190.
14. Landis, E. M.: Am. J. Physiol. **83**: 528, 1927-1928.
15. Schiller, A. A.: M. Clin. North America **36**: 201, 1952.
16. Tedeschi, C. G.: Riv. sper. freniat. **56**: 497, 1932.
17. Carleton, A., Elkington, J. S., Greenfield, J. G., and Robb-Smith, A. H. T.: Quart. J. Med. **11**: 203, 1942.
18. Vogel, F. S., and McClenahan, J. L.: Am. J. Path. **28**: 701, 1952.
19. Ingalls, T. H., and Tedeschi, C. G.: Congenital Cranial-Encephalic Defects Associated With Vascular Anomalies in the Progency of Mice Exposed to Anoxia During Pregnancy. To be published.
20. Robbins, S. L.: Boston M. Quart. **3**: 7, 1952.
21. Potter, E. L.: Arch. Path. **46**: 87, 1948.

THE EFFECTS OF MATERNAL NARCOTIC ADDICTION ON THE NEWBORN

MILTON J. GOODFRIEND, M.D., F.A.C.S., IRVING ALFRED SHEY, M.D., AND MILTON D. KLEIN, M.D., F.A.C.S., NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology, Morrisania City Hospital)

IN RECENT years the increased use of narcotics among teen-agers and young adults has been widely publicized. Our attention was further focused on the problems of addiction when a local agency questioned the senior author on the possible effects of maternal morphinism on the newborn.

As we searched for such cases and discussed this problem with other obstretricians and pediatricians we were able to find 10 cases of pregnancy complicated by drug addiction. Five of these women were admitted to the obstetrical service of the Morrisania City Hospital during the years 1951 to 1954. Since the effects of narcotic withdrawal were not always characteristic in the cases under our observation, we checked the standard texts in pediatrics and obstetrics and the current literature, but were unable to gather much information. The United States Public Health Service and the World Health Organization at Geneva were contacted but they could offer us little help. Because of the paucity of available information we feel that a thorough review of this subject is timely.

Table I lists the number of cases reported in the literature of infants delivered of narcotic-addicted mothers, the symptoms reported, and the therapy given. Some of the infants were entirely asymptomatic. Those infants who develop abstinence symptoms, however, show a characteristic syndrome. Most authors have reported that the infant appears normal at birth, but within 24 to 72 hours a progressive restlessness and irritability begin. Accompanying the restlessness is a protracted shrill cry that may last for hours at a time and gives the impression that the infant is in pain. The infants feed poorly and the small amount of nourishment taken by mouth is usually vomited. Other authors have reported that yawning and intermittent cyanosis are frequently seen. Diarrhea occurs and together with the poor intake causes inanition. The infants undergo severe dystrophy and may die in convulsions. Generally speaking, the symptoms prominent in the newborn are very similar to those found in the abstinence syndrome of the adult.

It is readily understandable how somatic requirements for opiates can be built up in the fetus. It is well known that morphine readily passes the placenta and produces varying degrees of asphyxia in utero as indicated by changes in rate and rhythm of the fetal heart. Shute and Davis,[20] however, felt that individual susceptibility played an important role in the effects of

TABLE I. SUMMARY OF CASE HISTORIES RECORDED IN THE LITERATURE OF INFANTS BORN OF ADDICTED MOTHERS

YEAR	AUTHOR	NO. OF CASES	NUMBER SYMPTOMATIC	NUMBER ASYMPTOMATIC	TYPE OF SYMPTOMS	TIME OF ONSET	THERAPY
1892	Happel[1]	12	12	0	Progressive restlessness and cyanosis	2-3 days	20 drops of paregoric every 3 hours
1899	Tate[2]	4	4	0	Marked restlessness except after nursing	2-3 days	Mother's milk with mother continued on opiates
1900	Happel[3]	5	5	0	Progressive restlessness and cyanosis	2-3 days	20 drops of paregoric every 3 hours or 0.5 Gm. Dover's powder every 2 hours
1903	O. D.[4]	1	1	0	Progressive restlessness, hyperirritability, continuous crying for 48 hours, diaphoresis	2 days	1/120 grain morphine sulfate every other day
1909	Jennings[5]	3	2	1	Continuous shrill cry, restlessness, yawning, diaphoresis	At birth	Tincture of laudanum
1912	Pettey[6]	30	30	0	Restlessness, crying, progressive dehydration, collapse	3 days	18 drops paregoric every 4 hours; tincture of laudanum
1912	Reische[7]	1	0	1	—	—	—
1914	Ashworth[8]	5	5	0	"Withdrawal symptoms as in adult"	1 day	—
1920	Burnett[9]	8	8	0	Vomiting, restlessness, yawning, diarrhea	1 day	Paregoric for the first three days; then infant nurses with mother on opiates
1921	Bishop[10]	1	1	0	"Withdrawal symptoms"	1 day	Morphine
1930	Müller[11]	1	0	1	—	—	—
1930	Langstein[12]	4	4	0	Marked restlessness, cyanosis, continuous cry, vomiting, hyperreflexia, progressive dystrophy	1 day	Small doses of opium; infusions
1934	Menninger-Lerchenthal[13]	50	50	0	Restlessness, diarrhea, convulsions, collapse	2-3 days	Morphine; infant to nurse while mother continues to take opiates
1934	Terwilliger and Hatcher[14]	1	1	0	Restlessness, continuous cry, yawning, spasticity	1 day	Tincture of opium; morphine by injection

TABLE I—CONT'D

YEAR	AUTHOR	NO. OF CASES	NUMBER SYMPTOMATIC	NUMBER ASYMPTOMATIC	TYPE OF SYMPTOMS	TIME OF ONSET	THERAPY
1934	To and Oh[15]	29	29	0	Yawning, lacrimation, insomnia, weakness, diaphoresis, salivation	1 day	Mother blows opium smoke in infant's face or infant inhales opium smoke directly
1934	Pohlisch[16]	58	35	23	Restlessness, continuous cry, yawning, cyanosis	1-3 days	Opiates for the first three days; then nurses while mother continues opiates
1948	Pearlstein[17]	1	1	0	Restlessness, irritability, vomiting, diarrhea, and convulsions	3 days	Phenobarbital
1941	Pehu[18]	1	1	0	Violent cry, vomiting, lacrimation, diaphoresis, restlessness	At birth	Morphine by injection
1950	Burthiault[19]	1	1	0	Violent cry, restlessness, yawning, diaphoresis, diarrhea	2 days	Morphine and barbiturates

morphine, for observations on 300 mothers given morphine during labor showed that the 22 infants who showed signs of asphyxia did so disproportionately to the amount of morphine given. Their studies on placentas indicated that the placenta does not retain morphine and is not an important barrier to its passage.

Accordingly, opiates may enter the circulation of the fetus freely and depending on the frequency and dosage will produce in the newborn child the somatic changes present in addicted mothers. Edgar[21] reported that even in intrauterine life a curious restlessness develops similar to that seen after delivery. He reported violent intrauterine fetal movements just prior to the time when the mother required a dose of opiates and that soon after the narcotics were taken the fetal movements became normal. Because fetal movements were so turbulent he advised that attempts at cure of the mother during pregnancy should be limited to the first five months of gestation.

In the literature the successful treatment of withdrawal symptoms in the newborn was predicated on early recognition. Table I lists the various forms of treatment described. In essence, sedation must be given in the form of opium derivatives with individual doses depending on the infant's requirements. Opiates given orally, by injection, or by inhalation seem equally effective. Pearlstein[17] and Nicholas[22] used barbiturates with great effectiveness. Many authors felt that infants could be maintained symptom free on mother's milk provided that the mother continued to receive adequate dosage of opiates. Terwilliger and Hatcher,[14] and Kwit and Hatcher,[23] however,

could not isolate morphine from mother's milk despite large doses of morphine given to the mother. Since they felt that the drug could not be transmitted through the milk it was difficult to account for the apparent clinical effectiveness of mother's milk in eliminating the abstinence syndrome in the newborn. Shute and Davis[20] and Reische,[7] however, felt that it is possible that morphine may be chemically changed in the body so that it could not be extracted as morphine, yet in its converted form was adequate to prevent symptoms.

Finally, it was recommended that cure be attempted in the mother and the infant 3 to 4 months following delivery. Both should be hospitalized and gradually diminishing doses of opiates given. It was easy to cure the infant, for psychic dependence did not exist.

The following cases of pregnancy complicated by drug addiction were seen at the Morrisania City Hospital.

CASE 1.—E. B., a 19-year-old white primipara, was admitted to the hospital at term in active labor on Jan. 5, 1951. On questioning it was revealed that when five months pregnant she began to take heroin daily by the intravenous route and within a short time required 1 Gm. per day. Several weeks prior to term she attempted a cure by substituting dolophine in a dose of 15 to 30 mg. daily. During this period she suffered no untoward effects and was not conscious of unusual fetal activity. On admission it was noted that the scleras were icteric, but since the patient was in active labor work-up was deferred until after delivery. She was sedated with 100 mg. of Demerol and was delivered of a living female child that cried immediately. The infant was observed carefully throughout her ten-day stay in the hospital but failed to show unusual symptoms. She was discharged to the custody of a welfare agency. Following delivery, physical findings and laboratory work-up disclosed that the mother had infectious hepatitis. Following improvement in this condition the mother was referred to the guardianship of the Wayard Minor's Court.

It is understandable that the infant was asymptomatic in view of the elimination of heroin intake in the mother for several weeks prior to delivery. Infectious hepatitis is frequently seen in narcotic addicts because of the common use of contaminated needles and this probably was the source of this patient's infection.

CASE 2.—S. R., a 23-year-old Negro primiparous patient, was admitted to the hospital in active labor on Feb. 25, 1952, in the thirty-seventh week of gestation. The patient had been addicted to heroin for over a year, and in the third month of pregnancy was confined to the Women's House of Detention. Except for the week when she was in prison where she underwent enforced abstinence, she took heroin regularly, using 1 Gm. intravenously every other day. The last dose was taken two days prior to admission. On arrival at the ward there were no unusual physical findings and during an uneventful labor she was given 100 mg. of Demerol. She was delivered of a 6 pound 14 ounce living female child that cried spontaneously. In view of the mother's history the infant was given 1/16 grain of phenobarbital three times daily for prophylactic reasons. The child appeared normal and took her feedings well. No unusual symptoms were observed during the five-day hospital stay. Follow-up during the first year showed that the infant developed normally.

We have no way of knowing whether or not this infant would have developed abstinence symptoms in view of her sedation with phenobarbital.

CASE 3.—J. J., a 22-year-old Negro primipara was admitted to the medical service in the thirty-sixth week of gestation on Nov. 21, 1952, with yellow sceleras, dark urine, and clay-colored stools. The history disclosed that she had been taking 1 grain of heroin daily via the intravenous route, with the last dose taken ten days prior to hospitalization. Physical findings and laboratory data substantiated a diagnosis of infectious hepatitis complicating pregnancy. Shortly after admission she developed strong uterine contrac-

tions and was then transferred to the obstetrical service. After a short labor she was delivered of a living female child that weighed 4 pounds 8 ounces. The infant thrived and showed no withdrawal symptoms during the two-week hospital stay. The mother was not given opiates during her hospitalization and developed no abstinence symptoms. She was discharged after the infectious hepatitis improved. Follow-up two months postpartum showed the infant to be developing satisfactorily but the mother was again taking heroin.

This is another case of infectious hepatitis probably transmitted by contaminated needles. The lack of abstinence symptoms in the newborn was possibly due to the fact that the mother had taken no heroin for ten days prior to delivery.

CASE 4.—A. L., a 20-year-old Negro gravida iii, para ii, was admitted to the hospital at term in active labor on Dec. 9, 1953. She stated that at age 16 while still in high school she became addicted to heroin and took 1 grain daily. Her two previous pregnancies were uneventful and both children were apparently normal. She had never told the obstetrician of her addiction. During the seventh month of the current pregnancy she attempted a cure of her addiction under medical supervision and took diminishing doses of morphine, so that her last dose was taken six weeks prior to admission. Labor was rapid and she delivered a living female child that cried immediately. Opiates were withheld from mother and infant, and no adverse symptoms developed during the five-day hospital stay.

Again the absence of symptoms in the infant was probably related to the long interval between the last dose of opiate and the time of delivery.

CASE 5.—A. A., a 19-year-old Negro primigravida, was admitted to the obstetrical ward on April 5, 1954, in the seventh month of gestation complaining of chills and abdominal cramps of twenty-four hours' duration. At this time she volunteered the information that she was a heroin addict. She began using narcotics in November, 1952, and in May, 1953, she and her husband underwent treatment. By October, 1953, she was discharged as cured. In November, 1953, she was three months pregnant and registered at the clinic, but said nothing of her addiction. By December, 1953, she resumed the use of narcotics and was soon taking ½ to 1 grain of heroin daily intravenously. She took her last dose the day prior to admission. Physical examination showed no unusual findings and laboratory data were essentially negative. She was given 3 grains of Seconal and symptoms subsided. On the fourth hospital day she released herself from hospital care and was not seen again until she returned in labor on May 11, 1954. She claimed that she had taken no drugs in the five weeks between admissions. After a short labor she delivered a living male child that weighed 5 pounds 5 ounces. Opiates were withheld from both mother and infant but no abstinence symptoms ever developed during their five-day hospital stay. In view of the period of 5 and one-half weeks wherein no opium derivatives were used, it is understandable that the infant was asymptomatic.

Cases 6-10 were seen at the Harlem Hospital and are presented by permission of Dr. Harry J. Cohen, Director of Pediatrics.

CASE 6.—S. M., a 23-year-old Negro gravida iii, para ii, was admitted to Harlem Hospital on Jan. 13, 1954, after a precipitate delivery at home in the thirty-second week of gestation. The infant weighed 4 pounds 8 ounces and appeared to be in good condition. The mother volunteered the information that she was a drug addict who would stay in the hospital only if she were provided with opiates. When told that she would have to be transferred to effect a cure she signed out. The infant remained asymptomatic until the third postpartum day at which time it developed progressive irritability, generalized tremors, loose stools, and a continuous shrill cry. Irritability was so extreme that the legs had to be restrained to prevent severe excoriation of the heels. Treatment consisted of elixir of Luminal, ¼ grain per dram, 10 drops four times a day, and one drop of paregoric four times a day. The irritability and tremors diminished over a period of four days and medication was discontinued. While there were minimal symptoms thereafter,

the infant began to feed well and gained weight. He was discharged after 28 days of hospitalization weighing 5 pounds 6 ounces. The mother was completely uncooperative and would not permit examination of the child on a follow-up home visit.

In this case the infant's symptoms were probably present because the mother was taking opiates until the time of her delivery, and her refusal to stay in the hospital showed her marked dependence on the opiates unavailable to her.

CASE 7.—D. B., a 24-year-old Negro primipara, was admitted at term in active labor on Jan. 24, 1954, and was delivered by low forceps of a living male child that weighed 5 pounds 4 ounces. The mother was a known heroin addict but would not give a detailed history. She was given no opiates during her five-day hospital stay and developed irritability and occasional vomiting. The infant appeared normal for the first two days post partum and then developed progressive irritability, a shrill continuous cry, and would not take his feedings. Ten drops of elixir of Luminal were given three times daily following which symptoms subsided rapidly. Within forty-eight hours the infant appeared symptom free. He was discharged in the custody of the mother on the fifth postpartum day. Follow-up two weeks later showed the infant to be feeding well and growing normally.

In this case both the mother and infant showed signs of abstinence. Prompt treatment caused a rapid cessation of symptoms in the newborn.

CASE 8.—N. D., a 20-year-old Negro primigravida, was admitted in active labor on Feb. 19, 1954, and was delivered spontaneously of a 6 pound 8½ ounce living female child after a short labor. The mother was a known heroin addict and showed signs of restlessness several hours post partum. She became noisy, hyperirritable, and walked off the ward. When no opiates were permitted she signed out on the day following delivery. The infant showed signs of asphyxia immediately after birth. Respirations were grunting in type and moist râles were heard in the right upper chest. Coarse tremors of the extremities were noted. The child was placed on antibiotics and given oxygen. On the following day she became progressively more irritable, developed marked tremors, and had a continuous shrieking cry. Calcium gluconate and elixir of Luminal were given, but despite medication the infant did not respond. She became cyanotic at intervals and the temperature rose to 104° F. Marked irritability and coarse tremors persisted. The infant became progressively dehydrated despite parenteral fluid therapy and died seventy-two hours after delivery. Autopsy by the medical examiner showed right upper lobe pneumonia.

We feel that the symptoms shown by this infant were not entirely explained by the pneumonia. It is also our impression that some of the infant deaths reported as due to cerebral anoxia and cerebral hemorrhage may possibly be due to other causes, especially when the symptoms are similar to those of the abstinence syndrome.

CASE 9.—J. O., a 27-year-old Negro primigravida, was admitted in active labor on Feb. 6, 1954, and was delivered spontaneously of a living female child that weighed 6 pounds 6 ounces. She was a known heroin addict but further history was not obtained. She became extremely restless and irritable on the day following delivery and began to vomit. She was given 2 grains of Nembutal three times daily and although her symptoms subsided somewhat she remained hyperirritable and signed out seventy-two hours after admission. The infant appeared normal for the first twenty-four hours, following which she developed tremors of the extremities, twitching of the facial musculature, marked irritability, and an almost continuous screaming cry. Ten drops of elixir of Luminal were given four times a day and symptoms abated rapidly. The infant, however, was signed out by the mother on the third postpartum day. Follow-up could not be made for the mother gave an incorrect address and could not be traced.

CASE 10.—B. J., a 20-year-old Negro gravida ii, para i, was admitted on July 23, 1954, after a precipitate home delivery of a living male child that weighed 6 pounds 2 ounces. Twenty-four hours post partum the infant began to vomit, developed coarse tremors, and showed extreme irritability. Suspecting "concealed" morphinism, the pediatric resident questioned the mother and elicited the history of heroin addiction with the last dose taken

intravenously the day prior to delivery. The infant was given elixir of Luminal four times daily and gradually became quiet and took feedings well. The mother developed no symptoms of withdrawal and was discharged on the fourth hospital day. She signed the infant out against advice. The infant appeared normal on a follow-up home visit.

Comment

While the abstinence syndrome in the newborn is an uncommon condition it is our impression that it occurs more frequently than is reported in the literature. Unless a careful history is taken the patient does not usually divulge the information that she is an addict, knowing the social stigma resulting therefrom. In two of our cases the presence of infectious hepatitis gave us the lead to the history of addiction, and in one case the presence of symptoms in the infant led the physician to suspect maternal addiction. If addiction is kept in mind, the diagnosis will be relatively easy. The importance of making the diagnosis early and treating the infant effectively is readily apparent from the literature. The over-all reported mortality in infants showing withdrawal symptoms was 33.8 per cent, and in cases where the condition remained unrecognized and no treatment was given 93.2 per cent died.

We can explain the varying degrees of withdrawal symptoms in the infant only by the variation in degree of addiction in the mother. If treatment is instituted for several weeks prior to delivery, it is likely that the infant will show no abstinence symptoms. If the mother takes large doses of opiates until the very end of pregnancy it will be more likely that the infant will be a narcotic addict at birth. A complicating factor is the known technique of "cutting" the dose sold to addicts so that the mother might not be taking as much as she thinks. This might explain why mothers supposedly taking ½ to 1 grain of heroin a day give birth to asymptomatic infants and themselves develop minimal symptoms of abstinence in the hospital where no opiates are given. In any case, if the use of narcotics in women of the childbearing age continues to rise, the problem of addiction in the newborn will become increasingly important and the obstetrician and pediatrician should be aware of its existence.

Summary and Conclusion

1. Narcotic addiction with abstinence symptoms is a distinct clinical entity in the newborn.

2. The symptom complex seems to bear a distinct relationship to the duration of addiction in the mother, the quantity of drug used, and the time of the last dose of narcotic prior to the birth of the child.

3. Early diagnosis is important. Addiction in the mother should be suspected even in the absence of a history, if the infant shows signs suggestive of narcotic withdrawal.

4. Recommended treatment consists of morphine derivatives and/or barbiturates.

5. Ten cases are hereby reported which demonstrate the various degrees of symtomatology.

We wish to thank Dr. Harry J. Cohen, Director of Pediatrics at Harlem Hospital, and Dr. Gene Ann Polk, Resident in Pediatrics, for their help in obtaining the reports of Cases 6-10.

References

1. Happel, J. J.: Tr. M. Soc. Tennessee p. 162, 1892; M & S Reporter, Philadelphia, **67**: 402, 1892.
2. Tate, Magnus: Cincinnati Lancet-Clinic **43**: 598, 1899.
3. Happel, J. J.: J. A. M. A. **35**: 47, 1900.
4. O. D.: Queries and Minor Notes, J. A. M. A. **40**: 1092, 1903.
5. Jennings, Oscar: J. Inebriety, Boston, **31**: 101, 1909.
6. Pettey, G.: Memphis M. Month. **32**: 57, 1912.
7. Reische, A.: Ztschr. f. Kinderh. **4**: 542, 1912.
8. Ashworth, W. C.: South. M. J. **7**: 487, 1914.
9. Burnett, S. G.: M. Herald and Electro Therapist **39**: 161, 1920.
10. Bishop, Ernest: The Narcotic Drug Problem, New York, 1921, The Macmillan Company, p. 21.
11. Müller, O.: Med. Klin. **26**: 815, 1930.
12. Langstein, Leo: Med. Klin. **26**: 500, 1930.
13. Menninger-Lerchenthal, E.: Monatsschr. Kinderh. **60**: 182, 1934.
14. Terwilliger, W. G., and Hatcher, R. A.: Surg., Gynec. & Obst. **58**: 823, 1934.
15. To, S., and Oh, J.: Jap. J. M. Sc. Tr., IV. Pharmacol. **8**: 100, 1934.
16. Pohlisch, K.: Die Kinder männlicher und weiblicher Morphinisten. Leipzig, 1934, Georg Thieme.
17. Pearlstein, M. A.: J. A. M. A. **46**: 6, 1948.
18. Pehu, M.: Ann. Pediat. **159**: 240, 1942.
19. Burthiault, R.: Pédiatrie **5**: 234, 1950.
20. Shute, E., and Davis, M.: Surg., Gynec. & Obst. **57**: 727, 1933.
21. Edgar, J. C.: Practice of Obstetrics, ed. 5, Philadelphia, 1916, P. Blakiston's Son & Co.
22. Nicholas, M.: Contribution à l'étude du morphinisme du nouveau-né, Thesis, No. 145, Lyon, 1950.
23. Kwit, N., and Hatcher, R.: Am. J. Dis. Child. **49**: 900, 1935.
24. Weiss, R. F.: Med. Klin. **26**: 1192, 1930.

POSTPARTUM HEMORRHAGE

Etiology and Management

ABRAHAM SHULMAN, M.D., AND WILFORD J. RATZAN, M.D., PATERSON, N. J.,
PAUL GROSSBARD, M.D., PASSAIC, N. J., AND ARTHUR C. LAWRENCE, M.D.,
PATERSON, N. J.

(From the Departments of Obstetrics and Gynecology, Barnert Hospital, Paterson, N. J., and Beth Israel Hospital, Passaic, N. J.)

POSTPARTUM hemorrhage is one of the major causes of maternal mortality. Successful management requires accurate diagnosis of the cause and prompt, adequate therapy with due regard to physiologic considerations.

We have studied 100 cases of postpartum hemorrhage occurring in the Departments of Obstetrics and Gynecology of the Barnert Memorial Hospital in Paterson, New Jersey, and Beth Israel Hospital in Passaic, New Jersey, during the period of July, 1952, to July, 1954. Their etiology, management, and ultimate outcome will be briefly discussed with particular reference to several unusual cases.

General and specific criteria were established for the selection of cases to be included in this study. We have included those cases in which the clinical evaluation of blood loss was over 500 c.c. at the time of delivery or over 600 c.c. in the first 24 hours after delivery, and those cases in which the patient's pulse rate, blood pressure, and hemoglobin estimation reflected blood loss. Regardless of specific criteria, we have postulated the existence of postpartum hemorrhage when the manifest bleeding was sufficient to warrant, in the opinion of the obstetrician, the administration of whole blood, plasma, packing, or any combination of these therapeutic agents. The 100 cases studied represent 2.8 per cent of the total number of patients (3,519) delivered in these institutions during the two-year period selected for study.

Management of this obstetric complication involves some appreciation of the relationship of blood loss and attendant symptoms to normal circulating blood volume. The circulating blood volume in any given patient bears a rough relationship to the body weight. In a pregnant patient weighing 120 pounds, the blood volume is about 4,000 c.c.; in a patient weighing 150 pounds, about 5,000 c.c. An estimated loss of 10 per cent of total blood volume may be considered obstetrical hemorrhage, although clinical symptoms may not be apparent. A loss of 20 per cent will be reflected by definite physical signs; an estimated loss of 30 per cent usually results in collapse. The patient's response to blood loss may be immediate or delayed and this response is modified by pre-existing conditions such as the hemoglobin status at the time of delivery, state of hydration, exhaustion, etc., at the beginning of the hemor-

rhage. All these factors must be taken into consideration in evaluating the amount of replacement therapy required and the rapidity of administration of such therapy.

In reviewing these 100 consecutive cases, we have divided them for convenience into the classification of early and late postpartum hemorrhage.

Early cases are defined as those occurring immediately after the third stage of labor. There were 85 such cases (Table I).

TABLE I. CAUSES OF EARLY POSTPARTUM HEMORRHAGE

Cervical laceration	34
Vaginal laceration	24
Relaxed uterine fundus	9
Atony of uterus	8
Primary uterine inertia following delivery of a molar pregnancy	1
Third-degree perineal laceration	3
Inversion of uterus	1
Partial placenta accreta	2
Unexplained	3

Fifteen cases were classified as delayed hemorrhage, i.e., hemorrhage more than one hour after termination of the third stage of labor (Table II).

TABLE II. CAUSES OF DELAYED POSTPARTUM HEMORRHAGE

Retained secundines	9
Hematomas	3
Bleeding following anticoagulant therapy	1
Afibrinogenemia	2

Analgesia during labor was accomplished with Demerol, with or without scopolamine, or by caudal analgesia. Delivery was effected under caudal, saddle block, or inhalation anesthesia.

Cervical Laceration.—This was the cause of 34 cases. Twenty-one of these patients were para 0 or i; 13 were para ii to vi. Cervical laceration occurred almost equally at the various ages from 18 to 40. There were 4 cases in the age group 35 to 40. The average duration of the first stage of labor in this group was 10 hours for primigravidas, and 7 hours for multigravidas. The average duration of the second stage of labor was 1½ hours in primigravidas and ¾ to 1 hour in multigravidas. Twelve cases of cervical laceration followed midforceps delivery with rotation of the baby's head, 16 cases followed midforceps delivery without rotation, 3 cases occurred following sudden precipitate progress in labor, and 2 occurred in spontaneous deliveries. Seventeen patient (50 per cent) had been treated with dilute Pitocin infusion for elective induction of labor or to expedite labor already in progress. Four patients in the whole group gave a history of previous traumatic delivery followed by transfusion therapy. One was delivered vaginally in spite of a previously performed amputation of the cervix. This patient presented the most alarming hemorrhage in this group.

The diagnosis of cervical laceration was made by inspection in all cases. Treatment consisted of suture of the laceration in 32 cases, 26 with packing and 6 without, and simple packing in 2 cases. One unit (500 c.c.) of blood was required in 24 cases and 4 units in 2 cases, plus subsequent infusions of water and saline solution. There were no deaths and only one instance of postpartum morbidity in this group with cervical lacerations.

Vaginal Lacerations.—There were 24 vaginal lacerations, 17 in primiparas, and 7 in multiparas. The majority (21) occurred in the 18 to 30 year age group, 3 in the 30 to 40 year age group, one of these in a primigravida of 37. The average duration of the first stage of labor was 12 hours for primigravidas and 9 hours for multigravidas. The second stage averages 2 hours for primigravidas and 1 hour for multigravidas. Three patients had a history of previous traumatic vaginal deliveries. Twenty-five per cent of the 24 patients had received a Pitocin infusion during labor. Vaginal laceration occurred in 18 cases (75 per cent) following the application of midforceps with rotation of the occiput; 4 cases (17 per cent) followed the application of midforceps without rotation; and 2 cases (8 per cent) followed spontaneous deliveries. Four cases occurred following delivery in a para i or para ii without episiotomy, 8 cases followed median episiotomy, and 12 followed mediolateral episiotomy. Six of these lacerations occurred in patients whose physical status and clinical behavior in labor suggested the diagnosis of dystrophy-dystocia syndrome.

The diagnosis was made immediately after delivery by inspection in all but 2 cases. These latter 2 instances of hemorrhage due to vaginal laceration became apparent after removal of a previously inserted vaginal packing. One unit of blood was administered in 16 cases in this group. All of them were treated by adequate suturing of the laceration. In addition, 20 patients had supplementary vaginal packing inserted. There were no maternal deaths and no morbidity in this group. Two patients subsequently developed vaginal synechiae as a consequence, presumably, of the packing.

Relaxed Fundus.—This was the cause of hemorrhage in 9 cases. In this group we classify those patients whose fundi relaxed with accompanying hemorrhage but responded promptly and well to uterine massage, oxytocics, or both. Three cases occurred in primigravidas, 6 in multigravidas. The age of the patients varied from 22 to 37 years. In 2 cases, the first stage of labor was less than 6 hours. In all cases, the second stage varied from ¾ to 1½ hours. Relaxed fundus appeared in 3 patients whose delivery was accomplished by difficult midforceps application, the remainder followed delivery with low forceps. There was no history of traumatic deliveries or prolonged labor in previous pregnancies. Two patients gave a history of previous precipitate labor. A Pitocin infusion had been given during labor in all cases in this group except two. In 4 of them, the Pitocin infusion was discontinued before the termination of the third stage of labor. Delivery was accomplished under caudal anesthesia in 1 case, inhalation anesthesia in 2, and saddle block anesthesia in 6.

Treatment consisted of the following measures: the administration of oxytocics (Ergotrate and Pitocin) intramuscularly and intravenously, manual massage of the fundus, transfusions and fluids intravenously. One patient required the administration of two units of blood and the continuous administration of a Pitocin infusion coupled with manual massage for thirty minutes before the fundus remained well contracted. There was no maternal morbidity or mortality in this group.

Uterine Atony.—This accounted for 8 cases. We have classified in this group, according to the criteria of Mengert, those cases of primary uterine hemorrhage which did not respond promptly to massage or oxytocics. Three of these cases occurred in primigravidas and 5 in multigravidas. One patient developed atony after delivery of a multiple pregnancy. The patients' ages varied from 21 to 32. A prolonged first or second stage of labor characterized 8 of these cases. Six had a first stage of more than 18 hours and two a second stage of more than two hours. Five cases of atony followed midforceps deliveries. One patient had a history suggesting atony following a previous delivery. In 50 per cent of these cases. Pitocin infusion had been used before delivery to combat primary uterine inertia. The diagnosis of atony was made after

inspection of the cervix and vagina revealed no evidence of a bleeding laceration, the placenta appeared intact, and palpation of the fundus disclosed a large, boggy uterus.

All patients in this group were given transfusions and oxytocics (Ergotrate and Pitocin) intramuscularly and intravenously, as well as manual massage. One patient had a bilateral ligation of the uterine vessels and 6 were ultimately treated by supracervical hysterectomy. There were no postoperative sequelae in the cases of atony treated. One case of atony following delivery of a hydatidiform mole deserves consideration. This occurred in a 26-year-old para i, gravida ii, who spontaneously expelled a vesicular mass at 5 months of pregnancy. The expulsion was followed by excessive vaginal hemorrhage in the presence of a large, soft uterus. Manual exploration of the uterine cavity revealed no evidence of retained molar tissue. The patient was treated successfully with intrauterine packing, blood transfusion, and oxytocics.

Third-degree Laceration.—There were 3 cases of third-degree perineal laceration, which was characteristically accompanied by moderate rather than severe bleeding. Two cases followed midforceps delivery in a primigravida with a baby over 8 pounds, undertaken with a median episiotomy. The third case followed low forceps delivery of a 7½ pound baby in a primigravida whose median episiotomy suddenly extended down a short perineal body. These cases were treated with three layers of atraumatic sutures reconstructing the anterior rectal wall, sphincter muscles, rectovaginal septum, and the perineum. Two patients received one unit of blood. Postoperative care consisted of nonresidue diet, antibiotics, Sulfasuxidine, and mineral oil each night. There were no sequelae in any of these cases.

Inversion of the Uterus.—This occurred in one case. The patient was 28 years of age, para i, gravida ii, with a first stage of labor of 10 hours and a second stage of one hour. Delivery was effected by low forceps and median episiotomy. Pitocin had not been used in this case. Analgesia during labor consisted of Demerol and scopolamine. Anesthesia for delivery was saddle block. The previous pregnancy, labor, and delivery were without incident. Inversion of the uterus occurred shortly after several attempts to exercise a forcible Credé maneuver. The inverted uterus presented itself between the patient's thighs, with placenta attached. Profuse bleeding occurred, and complete collapse and shock became apparent. Therapy consisted of multiple transfusion (the veins could be located only by cutdown exposure), oxygen, Levophed intravenously, and infusions. As soon as the general condition improved somewhat, the patient was taken to the operating room. The placenta was peeled away from the endometrium, and gentle attempts were made to reposit the uterus. These were unsuccessful. A Huntington operation (laparotomy, with retraction of the inversion, using a vulsella) was then performed. The patient received more blood and Levophed during and after operation. She went on to complete recovery. Since then, she has had another pregnancy, labor, and delivery without difficulty.

Partial Placenta Accreta.—This was observed twice in this study in patients whose ages were, respectively, 25 and 37 years. The first patient was para i, gravida ii, and the second para iii, gravida iv. The duration of labor in each case was not remarkable and both deliveries were consummated by low forceps. The third stage of labor required less than 12 minutes in each case. The preceding histories were noncontributory and Pitocin infusion had been used to expedite labor in one of the 2 cases. The diagnosis was not made immediately in any case. The tentative diagnosis in each case was atony, after inspection of the cervix and vagina had yielded no clue as to the source of bleeding. Management consisted of oxytocics intravenously and intramuscu-

larly, packing, and the free use of blood which amounted to five transfusions in one of the reported cases. One case was ultimately treated with supracervical hysterectomy and one with bilateral ligation of the uterine vessels. The outcome in each case was excellent.

Unexplained.—There were 3 cases of unexplained postpartum hemorrhage. Review of these cases in terms of past history, parity, course of labor, type of delivery, etc., gives no clue as to the source of hemorrhage. Each patient was examined at the time of undue bleeding and apparently supplied no evidence of cervical or vaginal laceration and no evidence of retained secundines or atony. The uterus was well contracted and the abdomen was soft. These cases were treated successfully with transfusions and oxytocics.

Delayed bleeding was considered to have been caused by retained secundines, postpartum hematomas, anticoagulant therapy, and afibrinogenemia.

Retained Secundines.—This occurred 9 times. Three of the patients with this complication were primigravidas, 4 were para i, gravida ii, and 2 were para ii, gravida iii. The ages varied from 21 to 36 years. The duration of labor in each case was within normal limits and the type of delivery described as spontaneous or low forceps in all but 2 patients who were delivered by midforceps. One case of retained secundines followed a cesarean section. A Pitocin infusion was used in 3 cases during labor, 2 for elective induction and in the remaining case for the treatment of primary uterine inertia. Two patients had a history of retained secundines following a previous delivery. One patient had been discharged on the fifth postpartum day with the fundus described as 1½ to 2 fingers below the umbilicus. Two patients had been discharged on the fifth postpartum day with a moderate lochia rubra; otherwise the postpartum courses were uneventful. Seven cases of postpartum hemorrhage from retained secundines occurred between the seventh and fourteenth postpartum days and 2 cases between the fourteenth and eighteenth days. All cases were successfully managed with transfusion, dilatation and curettage, oxytocics, and intrauterine packing. The average amount of blood required in these cases ranged from 2 to 4 pints of whole blood.

Postpartum Hematomas.—These were observed in 3 patients. Two hematomas occurred about the labia and one hematoma was perineal in location. Two hematomas occurred in primigravidas, one an elderly primigravida, and one hematoma occurred in a patient who was para ii, gravida iii, with obvious vulvar varicosities. Two of the 3 primigravidas were delivered by midforceps of babies that weighed more than 8 pounds. Two of 3 hematomas occurred with mediolateral episiotomies and one followed a median episiotomy. One of the 3 hematomas occurred after a prolonged first stage, 21 hours, and a long second stage (i.e., more than 2 hours).

The average lapse of time before recognition of the situation in these cases averaged 2 to 10 hours. The diagnosis was made in each case by evidence of blood loss, distortion or dislocation of the perineum, anus, or vagina, and subjective complaints of severe localized pain. The average amount of blood used in therapy was 1 to 2 pints and all patients were successfully treated with evacuation of the hematoma, packing and/or suturing of the hematoma cavity, packing of the vagina, blood and antibiotics.

Bleeding Following Anticoagulant Therapy.—There was one case of delayed postpartum bleeding following anticoagulant therapy. The patient was a 28-year-old para i, gravida ii, who developed a pulmonary embolus spontaneously early in labor. Her labor was short, 5 to 6 hours, and was treated with early caudal analgesia, continuous oxygen, Luminal sodium by hypodermic, slow drip of intravenous Pitocin, and low forceps delivery early in the second stage. This patient was adequately treated with Dicumarol and heparin

immediately after delivery to prevent recurrence of the embolic phenomenon. There were no sequelae until about 14 hours after delivery when the persistent complaint of pain directed attention to a slowly developing labial hematoma. This was treated with one blood transfusion, evacuation of the hematoma, and packing of the hematoma cavity as well as the vagina. Anticoagulant therapy was immediately discontinued, the packing removed on the fourth postpartum day, and the remainder of the postpartum course was uneventful.

Afibrinogenemia.—Two cases of massive hemorrhage due to afibrinogenemia were recorded. Each one will be described separately.

The first patient was a 24-year-old para 0, gravida i, who was treated with elective cesarean section because of x-ray and clinical evidence of pelvic abnormalities. This patient was transfused at the beginning of the section because of a slightly lowered hemoglobin (10 Gm.). The section itself was uneventful. She developed gross vaginal hemorrhage 1 to 2 hours after completion of the section despite a well-contracted fundus. Repeated transfusions failed to alleviate her condition and shock and vaginal hemorrhage persisted. Three to four hours after termination of the section it was noted that the patient's blood failed to clot over a one-hour period of observation and a presumptive diagnosis of afibrinogenemia was made. Fibrinogen was secured promptly and 4 Gm. was administered intravenously. The vaginal hemorrhage ceased abruptly as soon as 3 to 4 Gm. of fibrinogen had entered the circulation. Despite cessation of hemorrhage, however, the patient remained in shock and further continued administration of blood resulted in pulmonary edema which, despite intensive therapy, was fatal. Death occurred 20 hours after the cesarean section and 11 hours after the hemorrhage had stopped following fibrinogen replacement.

The second patient was a 35-year-old para ii, gravida iii, whose past history was noncontributory except for a mild anemia in this pregnancy. Labor and delivery were uneventful but delivery of the placenta was followed immediately by profuse hemorrhage and shock. The only pertinent finding was some relaxation of the uterus. The situation was managed by dextran, intravenous Pitocin, 1,500 c.c. of blood, and packing of the uterus. The patient bled through the packing and a second packing was inserted but did not stop the bleeding. At this time, a supracervical hysterectomy was performed. Bleeding persisted in moderate amount for 24 hours after hysterectomy and fibrinogen determination done the day after supracervical hysterectomy was 60 mg. per cent. Whole blood was given again at this time. The second postoperative day was marked by more profuse vaginal bleeding and the fibrinogen level on this day was 80 mg. per cent. On the third postoperative day, she was given 2 Gm. of fibrinogen and within 24 hours bleeding from the cervical stump ceased entirely. The remainder of the postoperative course was complicated only by a mild cystitis. The blood fibrinogen level on discharge was 175 mg. per cent.

Comment and Summary

Several facts worthy of note have resulted from this study. The frequency of cervical laceration noted bears a rough proportion to the frequency of routine cervical inspection. The incidence of cervical laceration, moreover, has an approximate inverse relationship to the duration of the second stage of labor and has a more direct relationship to the frequency of traumatic deliveries. Spontaneous cervical lacerations occurring with precipitate labors are often more extensive than similar lacerations resulting from traumatic forceps deliveries. Prior cervical surgery must be carefully evaluated in terms of potential spontaneous laceration in a future vaginal delivery. The status of elderly primigravidas does not seem to be as important a predisposing factor in the causation of vaginal lacerations as traumatic deliveries, large babies, and the incorrect choice of episiotomy. Relaxed fundus may be due

to many etiological factors such as prolonged or precipitate labors, over-all condition of the patient, and traumatic deliveries. Whenever a Pitocin infusion is administered as therapy during labor, the incidence of relaxed fundus following delivery can be sharply decreased by maintaining the Pitocin well past the end of the third stage of labor. Third-degree laceration of the perineum usually follows traumatic delivery or poor evaluation of episiotomy. It is interesting to note that a properly repaired third-degree laceration followed by adequate postoperative care rarely affords any sequelae. Inversion of the uterus, a rare circumstance, may be treated vaginally or abdominally. In another case, previously encountered at our institution, the uterus was reposited vaginally with identically good results. A subsequent labor does not necessarily invoke again the pathologic factor that precipitated the inversion of the uterus previously.

The correlation of postpartum atony with primary uterine inertia in labor has appeared in this as well as in other series. The multiplicity of therapy used in our study suggests the need for individualizing the management of atony according to the age of the patient, her general condition, and parity.

Unexplained postpartum hemorrhage that responds to general therapy (blood and oxytocics) is intellectually provocative but rarely definitive. We feel that some of these cases may be due to an incomplete tear of the lower uterine segment or rupture of a broad ligament varix. Two of our 3 cases of unexplained hemorrhage might well have fitted into the category of incomplete uterine rupture.

Partial placenta accreta is a difficult diagnosis and is easily confused with the clinical picture of atony or retained secundines. Complete placenta accreta is more obvious inasmuch as failure of delivery of the placenta plus lack of bleeding suggests this diagnosis. Previously, supracervical hysterectomy was the only therapy advised. Bilateral ligation of the uterine vessels has given excellent results in one case in our series.

The diagnosis of retained secundines may be entertained while the patient is under hospital postpartum care. However, the masking effect of oxytocics administered in the hospital may delay the premonitory signs of retained secundines until the patient has left the institution. It is frequently impossible to ascertain whether secundines have been retained at the time of delivery except by manual exploration of the uterine cavity. Two patients in our series had experienced more than one incident of retained secundines, inferring a defect of uterine implantation or placental separation in the cases.

Postpartum hematomas are frequently preventable. Accurate hemotasis during suture of episiotomy, more routine choice of the median episiotomy where anatomically smaller blood vessels are present, avoidance of the pressure necrosis of prolonged labors and the trauma of difficult forceps deliveries are important factors in preventing hematomas. The difficulty of early diagnosis of a slowly spreading hematoma is obvious. The treatment of postpartum hematoma is well standardized and adequate.

Anticoagulant therapy has become more prominent in recent years and its use during and after labor is often lifesaving. The case of hemorrhage following such therapy reported here is unusual and should not contraindicate the use of anticoagulants where needed.

The possibility of afibrinogenemia should be suspected in any case of continuing profuse uterine hemorrhage without obvious cause. The diagnosis may be determined by examination of the clot in terms of formation, retraction, and dissolution, as well as by a blood fibrinogen level under about 150 mg. per cent, as this represents a minimal hemostatic level in the blood. The second case presented here was managed successfully on 2 Gm. of fibrinogen; it is frequently necessary, however, to administer a minimum of 4 Gm. to achieve adequate therapeutic results, and replacements of 8 to 12 Gm. of fibrinogen have been reported. The mechanism of death in most cases of afibrinogenemia is right heart failure and pulmonary edema consequent upon attempted rapid massive transfusion therapy. The earlier administration of adequate amounts of fibrinogen and more cautious use of massive transfusion therapy may well aid the prognosis in afibrinogenemia.

We believe the results reported here in a detailed study of 100 cases of postpartum hemorrhage have been due to the free use of new modalities and the focusing of attention on the causes and therapy of postpartum hemorrhage. The availability of large dosage of wide-spectrum antibiotics, massive transfusion therapy, intravenous Pitocin infusion as an oxytocic medicament, maintenance of fluid and electrolyte balance and hemostatic factors, varied anesthesia for poor-risk patients, and early resort to lifesaving surgery represent the sine qua non for successful management of postpartum hemorrhage.

POSTPARTUM HEMORRHAGE

A Five-Year Study at Queen of Angels Hospital

LEROY R. WEEKES, M.D., AND DANIEL M. O'TOOLE, M.D., LOS ANGELES, CALIF.

TO ME, there is but one obstetrical complication in the presence of which I must, at times, admit to actual panic. That complication is postpartum hemorrhage. This is particularly true in the presence of bleeding which one can not only see but also hear. I have known men far more experienced than I to be so completely unnerved in its presence that clear, sound judgment is lost. It is the complication which must always be feared as long as it is potentially present at every delivery.'' So says deCarle in beginning the discussion of Melody's paper on ''Primary Postpartum Hemorrhage.''[1]

Postpartum hemorrhage is defined[2] as bleeding from the birth canal in excess of 500 c.c. during the first 24 hours after delivery. Hemorrhages subsequent to the first 24 hours are called late hemorrhages and are outside the province of this discussion.

Predisposing factors are anemia, blood dyscrasias, insomnia at the end of pregnancy, exhaustion during labor, precipitate labor, overdistention of the uterus by multiple pregnancy or hydramnios, prolonged or deep anesthesia, and mismanagement of the third stage of labor. Most of these can be prevented or treated.

The over-all maternity mortality rate of 3.18 per 10,000 live births at Queen of Angels Hospital compares favorably with that of a general hospital like Cook County of Chicago[3] with a rate of 7.9 per 10,000. Since all the cases of maternal mortality from hemorrhage are considered preventable, full utilization of all the principles of proper management will bring continued improvement in mortality figures.

TABLE I. MATERNAL DEATHS AT QUEEN OF ANGELS HOSPITAL

YEAR	NUMBER OF DELIVERIES	NUMBER OF DEATHS	CAUSE OF DEATH		
			POSTPARTUM HEMORRHAGE	TOXEMIA	OTHER CAUSES
1949	4,503	2	1	1	0
1950	4,308	3	2	1	0
1951	4,391	2	0	1	1*
1952	4,428	2	1	0	1*
1953	4,529	2	0	1	1*
Total	22,159	11	4	4	3

*Other causes: cardiac failure, generalized carcinomatosis, aplastic anemia.

Table I shows a total of 11 deaths in 22,159 live births over a period of five years at Queen of Angels Hospital. The causes were: postpartum hemorrhage 4, toxemia 4, and other 3. The absence of any deaths from infection is

moot testimony of the efficacy of chemotherapeutic and antibiotic therapy. By the same token the 4 deaths from toxemia bring into bold relief the problem which toxemia still presents in spite of our continued investigation.

The following case histories present the maternal mortality due to postpartum hemorrhage in the Queen of Angels Hospital during the past five years.

CASE 1.—Mrs. S. O., a 23-year-old primipara, was admitted in labor. The first stage of labor lasted twelve hours and forty-five minutes, during which time she received Demerol and scopolamine. The patient was anesthetized with nitrous oxide, ether, and oxygen. A 7 pound 2 ounce boy was delivered with low forceps after a Kielland rotation from left occipitoposterior to right occipitoanterior position. Ergotrate $\frac{1}{320}$ grain, was administered intramuscularly during the delivery of the shoulders. The placenta was easily expressed five minutes following delivery. Pitocin, 10 I.U., was administered following the end of the third stage. The left mediolateral episiotomy was then repaired after the cervix and vagina were inspected and a vaginal pack was put in place. Thirty minutes following the delivery the patient suddenly lost 850 c.c. of blood from the uterus. The inhalation anesthesia was stopped, and oxygen was given. The patient promptly went into profound shock (blood pressure 30/0). Intramuscular Ergotrate, Trendelenburg position, 1,500 c.c. of whole blood, and intracardiac Adrenalin were of no avail. The patient died two hours and fifty-five minutes after delivery.

Comment.—The cause of death here was postpartum hemorrhage due to uterine atony secondary to a general anesthetic administered to a surgical level so that a surgical procedure—forceps rotation—could be performed. The resulting shock was irreversible from the start due to the great loss of circulating blood volume in spite of the ready availability and use of whole blood.

CASE 2.—Mrs. V. M., a 38-year-old gravida v, para iv, was admitted in labor at term with slight ankle edema, a blood pressure of 155/105, albuminuria (a trace), and polyhydramnios. Twenty cubic centimeters of 10 per cent magnesium sulfate was given intravenously and 2 grains of Luminal sodium intramuscularly, resulting in a fall of blood pressure to 136/88. Castor oil and an enema initiated labor. A sterile vaginal examination four hours after the onset of labor showed the cervix to be 4 to 5 cm. dilated. The membranes were stripped and amniotomy performed. The umbilical cord prolapsed over the fetal head but fortunately was replaced inside the lower uterine segment. The fetal heart tones dropped to 88 per minute. The patient was left on the delivery table and intravenous Pitocin started (10 I.U. in 500 c.c. of 5 per cent glucose). Complete dilatation was secured in one-half hour. A midforceps delivery was unsuccessfully attempted. Surgical anesthesia was induced with nitrous oxide, oxygen, and ether. An internal podalic version and extraction were done with a difficult delivery of the aftercoming head with Piper forceps. The baby weighed 10 pounds and 3 ounces, and after proper resuscitation was sent to the nursery for oxygen and heat. Following the delivery the mother promptly lost 1,200 to 2,000 c.c. of blood from the uterus. The placenta was manually removed, and the mother went into profound shock. She was given 500 c.c. of whole blood, 1,000 c.c. of plasma, intracardiac Adrenalin, Coramine, and Adrenalin intramuscularly to no avail. She died one hour and ten minutes after delivery. Autopsy disclosed a 10 cm. vertical laceration of the entire lower uterine segment. There was approximately 20 c.c. of clotted blood between the leaves of the left broad ligament.

Comment.—In this case there was prolapse of the cord which led the operator to continue in an effort to save the infant, even though conditions commonly required for version were not fulfilled. The error was then compounded by extraction, also despite what are normally considered contraindications. As a result the patient sustained an extensive laceration of the lower uterine segment which extended into the broad ligament with profuse hemorrhage and irreversible shock.

CASE 3.—Mrs. E. S., a 29-year-old gravida viii, para v, with a history of 2 induced abortions, was admitted in labor. The first stage of labor lasted 2 hours and the second

stage lasted 25 minutes. The delivery was an easy breech extraction under nitrous oxide, ether, and oxygen anesthesia. The cervix, vagina, and perineum were intact following delivery. The placenta was expressed five minutes after delivery, and Methergine, 1 c.c., was given intravenously after delivery of the baby. The patient promptly lost 500 c.c. of blood and went into shock. The uterus was packed, and 500 c.c. of whole blood given immediately. An ampule of Methergine was given intravenously one hour and twenty minutes after delivery and Pitocin intramuscularly because of the tendency of the uterus to relax. The patient rallied momentarily, but the pressure never rose above 70/50. The pack was removed and the uterus explored but no defect was found. She was given 3,000 c.c. of whole blood, 250 c.c. of plasma, but bleeding continued. The patient's condition failed to become stabilized, and she died five hours after delivery.

Comment.—This case presents a problem in analysis, because the reason for the hemorrhage and the progressive deterioration of the patient does not appear immediately apparent. Predisposing factors are a general anesthetic, a breech extraction, and multiparity. Although a hysterectomy was the treatment of choice because of the persistent uterine atony, the patient's condition never improved sufficiently to make operation possible without undue risk. A pre-existing anemia may have been a factor in the almost immediate onset of shock with a 500 c.c. blood loss. Perhaps, however, the blood loss was in excess of 500 c.c. but was misjudged by the obstetrician. This is an error to which we are all prone.

CASE 4.—Mrs. I. O., a 37-year-old gravida i, para 0, was admitted at 37 weeks' gestation and not in labor, with a blood pressure of 178/108, 3 plus edema of the ankles and knees, and urinary albumin 2.0 Gm. per liter. Since the patient failed to respond to conservative treatment for one week at home and intensive treatment for 24 hours in the hospital, a cesarean section was performed and was productive of a living 6 pound 3 ounce female infant. Two hours and thirty minutes after section, the patient began to bleed profusely from the vagina and the abdominal incision, and promptly went into shock. Blood transfusion was started immediately, followed by vitamin K, 30 mg., Ergotrate, and Pitocin. After massage of the uterus, the vaginal and abdominal bleeding appeared to be under control. Continuous blood transfusions were started. Two hours later, for no apparent reason, the patient slipped into profound shock, and in spite of stimulants she did not rally and died 12 hours later. An autopsy was performed and findings were consistent with late toxemia of pregnancy with massive postcesarean hemorrhage.

Comment.—This case resembles one of hypofibrinogenemia of pregnancy. Unfortunately, obstetricians were not as much aware of this condition in 1950 as they are now. As a result the patient was not studied hematologically. Unfortunately fibrogen replacement as stored whole blood is usually inadequate, and specific fibrinogen fractions are usually necessary.

Table II, which presents the number of deliveries and postpartum hemorrhages, shows a gradually decreasing incidence of this complication. This we feel is due in general to improved obstetric practices and more specifically to the increasing use of spinal anesthetic as compared to general anesthetic.

TABLE II. POSTPARTUM HEMORRHAGE

YEAR	NUMBER OF DELIVERIES	POSTPARTUM HEMORRHAGES	
		NO.	%
1949	4,503	46	1.20
1950	4,308	58	1.36
1951	4,391	23	0.54
1952	4,428	36	0.82
1953	4,529	37	0.81
Five-year total	22,159	200	0.9

From Table III it appears that the most common cause of postpartum bleeding is uterine atony. Much of the hemorrhage due to this cause can be prevented by the routine use of oxytocics. Heavy inhalation anesthesia should be eliminated as much as possible, for it greatly increases uterine atony. Many of the severe and fatal hemorrhages are due to extensive lacerations of the birth canal and less commonly to retention of placental fragments. In order to decrease the number of hemorrhages due to lacerations of the birth canal and retained placental tissue, some of the Staff men are performing routine postpartum manual exploration of the uterus and vagina. This has been done for the past two years without any special recourse to antibiotics and without any increased morbidity.

TABLE III. ETIOLOGY OF HEMORRHAGE

CAUSE OF HEMORRHAGE	NUMBER OF CASES	PER CENT
Uterine atony	151	75.5
Lacerations of birth canal	37	18.5
Retained placental tissue	12	6.0
Total	200	100.0

From Table IV it is quite obvious that general anesthesia carries a much higher risk of postpartum hemorrhage than conduction anesthesia. Dr. Jack C. Borel[4] of our staff recently reviewed a series of over 9,000 deliveries under spinal anesthesia with no serious complication. It is felt that the preferential and increasing use of spinal anesthesia on our service is in a large measure responsible for the low incidence of postpartum hemorrhage.

TABLE IV. HEMORRHAGE IN RELATION TO ANESTHESIA

YEAR	CONDUCTION ANESTHESIA	POSTPARTUM HEMORRHAGES		GENERAL ANESTHESIA	POSTPARTUM HEMORRHAGES	
		NO.	%		NO.	%
1949	2,594	19	0.7	1,883	26	1.4
1950	2,871	37	1.3	1,404	20	1.4
1951	3,181	13	0.4	1,158	9	0.8
1952	3,275	23	0.7	1,670	13	1.2
1953	3,385	23	0.7	1,090	13	1.2
Five-year total	15,306	115	0.7	7,205	81	1.1

Note.—Four of the 248 patients delivered without anesthesia had postpartum hemorrhage.

Management

Gordon[5] of Brooklyn, New York, has insisted for many years that hemorrhage is the major cause of maternal deaths. This he did even at a time when sepsis was statistically shown to be the most frequent cause. He demonstrated that in many cases hemorrhage played the deciding role in the patient's death, even though other causes were listed on the death certificate. His three-phase program—(1) anticipatory or preparatory, (2) preventive, and (3) active—is essentially the same as that observed at Queen of Angels Hospital with a few modifications.

The use of vaginal and uterine packs as a stopgap before hysterectomy is still controversial. Personally, I have not resorted to the uterine pack in the last five years, and fortunately I have not had to do a hysterectomy in cases of postpartum hemorrhage. My feeling is that the pack should be avoided since we have such excellent oxytocics for the control of atonic bleeding. Often the packing not only fails to stop the bleeding but may contribute to

death by lending a false sense of security as a result of the temporary cessation of blood flow. The manipulations associated with packing may stimulate temporary contraction of the uterus, only to be followed by ulceration and hidden bleeding. A pack may hinder rather than aid retraction of the uterus. Ten yards of 3 inch intrauterine gauze, when tightly packed, will absorb 1,000 c.c. of blood. Thus much valuable time and blood may be lost.

Use of the intrauterine pack should be restricted to cases of persistent postpartum hemorrhage in which facilities for laparotomy are not immediately available.

Those who pack the uterus for hemorrhage because of atony should never repeat it if the first pack fails.

Defibrinated Blood

More and more is being learned about the development during pregnancy of conditions making the blood incoagulable. Many physicians have observed cases in which the patient bled to death because the blood had lost the ability to clot. Hemorrhage came not only from the placental site, but from surgical incisions, venipunctures, and even from the nasopharynx, and in such cases death may have occurred despite heroic measures, including ample blood replacement and hysterectomy.

Since the report of Maloney and his associates[6] in 1949, a significant bibliography has accumulated on the subject of acquired afibrinogenemias of pregnancy. It is now known that wherever there is necrosis or degeneration at the placental site, there is a chance that particulate matter, thromboplastin, toxins, and anticoagulants can be absorbed into the maternal circulation. In extreme cases the woman's blood may become totally defibrinated and quite incoagulable. The hematologic findings include critically low values for fibrinogen and prothrombin and often a circulating fibrinolysin is present. Either a sample of such venous blood when incubated will not clot at all, or else the clot will be so fragile that the slightest vibration will cause it to disintegrate. When the plasma fibrinogen level is reduced from the normal concentration of 0.5 Gm. per 100 ml. to 0.2 Gm. per 100 ml. the circulating blood is incoagulable.

It is now known that abruptio placentae in particular, fetal death in utero, toxemia of pregnancy, and sometimes placenta previa may be associated with defibrination of maternal blood, depending upon the absorption of anticoagulants into the circulation. Women with these conditions should be studied hematologically as well as obstetrically. In addition to replacement of whole blood, specific deficiencies of fibrinogen and prothrombin must be eliminated if uncontrollable postpartum hemorrhage is to be averted.

A relatively pure fibrinogen fraction now available has been subjected to ultraviolet irradiation in an attempt to destroy the virus of homologous serum jaundice. This method of sterilization cannot always be relied upon. There is no assurance that this virus has been destroyed if it was present in the original plasma. In using this fibrinogen fraction, the physician must consider very carefully the danger of transmitting this virus to the patient and balance it against the danger of hemorrhagic complications.

Recommendations

It is imperative that all maternity hospitals have at lease one unit of Group O low-titer Rh-negative blood available at all times in the delivery room for immediate use.

If all hospitals had a recovery ward in which recently delivered patients could be kept for six or eight hours, some lives would be saved. After delivery, most obstetric patients are carefully watched for about 30 minutes in the delivery room, then returned to their rooms, and occasionally, a short time later, a patient is found to have had a profuse hemorrhage, a convulsion, or to be in shock. In the recovery ward, a nurse and a physician should be in constant attendance. This physician's duty should be to watch carefully the women just delivered. The patient's color and type of respiration can be observed, pulse rate counted, blood pressure taken, uterus palpated, amount of uterine bleeding observed, perineum inspected for a possible hematoma, and therapy administered in the form of hypodermic medication, intravenous fluids, and blood transfusions.

Summary

Postpartum hemorrhage has become the most important cause of maternal death. The clinical situations in which hemorrhage is likely to occur should be better known so that anticipatory and preventive treatment can be used before active treatment is necessitated. Most of the serious cases of postpartum bleeding are due to uterine atony, severe laceration of the birth passages, and retention of placental tissue. Much can be accomplished by eliminating traumatic deliveries and by more active management of the third stage. The establishment of obstetrical recovery rooms is strongly recommended. Recent knowledge about defibrination of the blood in women with degenerative changes at the placental site must be incorporated into the thinking of physicians dealing with obstetrical cases.

References

1. Melody, G. F.: California Med. **75**: 425, 1951.
2. Eastman, N. J.: Williams' Obstetrics, ed. 10, New York, 1950, Appleton-Century-Crofts Company, Inc., p. 912.
3. Fitzgerald, J. E., and Webster, A.: Am. J. Obst. & Gynec. **65**: 528, 1953.
4. Borel, J. C.: West. J. Surg. **62**: 22, 1954.
5. Gordon, C. A., Rosenthal, A. H., and O'Leary, J. L.: Am. J. Surg. **80**: 587, 1950.
6. Maloney, W. C., Egan, W. J., and Gorman, A. J.: New England J. Med. **240**: 596, 1949.
7. McLean, E. B.: Personal communication, Jan. 4, 1954.

POSTPARTUM HEMORRHAGE DUE TO A DEPLETION OF FIBRINOGEN FROM THE CIRCULATING BLOOD STREAM

MICHAEL KLEIN, M.D., F.A.C.S., JOHN I. BISKIND, M.D., AND ALBERT SILVERBERG, M.D., CLEVELAND, OHIO

(From the Division of Obstetrics and Gynecologyy, Mt. Sinai Hospital, Cleveland)

HYPOFIBRINOGENEMIA or afibrinogenemia is a hemorrhagic disease due to the absence or depletion of fibrinogen from the circulating blood with consequent loss of ability to clot. This may result from a congenital absence of fibrinogen due to error of synthesis, or a depletion of fibrinogen to a critical level due to a number of conditions directly related to pregnancy. The clinical state of this condition was first suggested as early as 1901 by DeLee. It has been only during the past decade, however, that the recognition of the physiological processes has been scrutinized and studied. The suggested etiological mechanisms are threefold: (1) Fibrinolytic enzymes enter the maternal sinusoids from necrotic decidua and destroy the circulating fibrinogen. (2) Thromboplastic material from the placenta or amniotic fluid enters the circulation causing intravascular clotting with depletion of fibrinogen. (3) Depression of fibrinogen production in the liver due to toxic fetal or maternal substances.

The most common predisposing factors associated with this condition during pregnancy or post partum are: (1) premature separation of the placenta, (2) amniotic fluid embolism, (3) presence of dead fetus in utero, (4) retained placental fragments, (5) eclampsia or severe pre-eclampsia, (6) surgical shock and other yet unknown conditions.

In the first three conditions mentioned, bleeding may be due to a secondary depletion of circulating fibrinogen which in turn may be the result of intravascular clotting. Such intravascular clotting has been demonstrated experimentally in animals by intravenous infusion of thromboplastin. It has been shown that the products of conception, when autolyzed, have strong thromboplastic activity similar to that of amniotic fluid or damaged tissue products.

A lytic enzyme has been shown to be present in circulating plasma at the time of delivery in a normal individual. During labor and for four to five hours post partum, the clot lysis time has been shown to be shortened from three days to a minimum of less than twenty-four hours.

The diagnosis of impending hypofibrinogenemia should be considered in the antepartum patient in cases of intrauterine death, pre-eclampsia, or unusual bleeding from the mucuous membranes, respiratory or gastrointestinal tract, or ecchymosis anywhere in the body. Repeated determinations of the plasma fibrinogen levels plus the following practical examination should be made.

1. Observation of the size or stability of the clot formed in a sample of uncitrated venous blood in the test tube. In a normal individual, the clot found is large and resists shaking. When fibrinogen is low or excessive fibrinolytic substance is present, the clot is small, the blood watery, and the initial clot may fragment or lyse in a matter of minutes.

2. A simple laboratory examination may be made by the addition of 0.9 ml. of venous blood to 0.1 ml. of bovine thrombin to determine very quickly the amount of fibrinogen depletion.

Treatment of Hypofibrinogenemia

In a case of hypofibrinogenemia without excessive fibrinolytic substance in the blood stream, the intravenous administration of 4 Gm. of human fibrinogen is usually sufficient to bring back the clotting time to normal and allay bleeding. The addition of whole fresh blood is used for replacement therapy. In those conditions where an excessive fibrinolytic substance is in circulation, as in one of the cases reported in this paper, the administration of whole blood and fibrinogen seems of little value since there is no definite way to determine how much circulating fibrinolytic enzyme is present or how to stop its production. In these cases it might be advisable, where bleeding cannot be controlled by blood and fibrinogen alone, to administer toluidine blue intravenously as an adjunct to the other therapy. This preparation has been reported to have an anti-heparinlike quality and may neutralize the fibrinolytic substance so that the added fibrinogen and whole blood may be effective. The reason for the ineffectiveness of whole blood alone is that fresh whole blood raises the fibrinogen level by only 10 mg. per cent. When therapy is effective, it might be advisable to have the patient under scrutiny for at least six days, since studies with radioisotopes have shown that when known quantities of fibrinogen are administered intravenously, about one-half disappears from the circulation in 5.6 days.

Prior to 1954, not a single case of hypofibrinogenemia was diagnosed at Mt. Sinai Hospital. Since then, 3 cases were diagnosed and treated with 2 maternal deaths resulting. There were 3,059 deliveries during 1954 at Mt. Sinai Hospital, giving an incidence of 1:1,000 delivered patients. The cases diagnosed as hypofibrinogenemia are here presented in detail.

CASE 1.—E. M., a 27-year-old Negro woman, para iii, gravida iv, was admitted at 1 A.M. on April 11, 1954, in early labor. This pregnancy was uneventful. The patient had gained a total of 13 pounds and her blood pressure never rose above 110/70. One-half hour after admission, she was given 1 c.c. Hykinone, 100 mg. of Demerol, 1/300 grain scopolamine, and 1½ grain of Seconal. Under 50 mg. of procaine spinal anesthesia, a living healthy female infant was delivered spontaneously at 5:28 A.M. The placenta was delivered in a matter of minutes. There was no excessive bleeding, nor was there any variation in the blood pressure.

About three hours after delivery, it was noted that the patient began to bleed profusely and passed large clots. The uterus was just below the umbilicus. A large amount of clots was expressed manually, but bleeding continued even with the administration of intravenous Pitocin. A diagnosis of uterine atony was made and the patient was taken to the operating room at 10 A.M. where a supracervical hysterectomy was done. No bleeding or oozing was encountered during or immediately after operation.

Fig. 1.

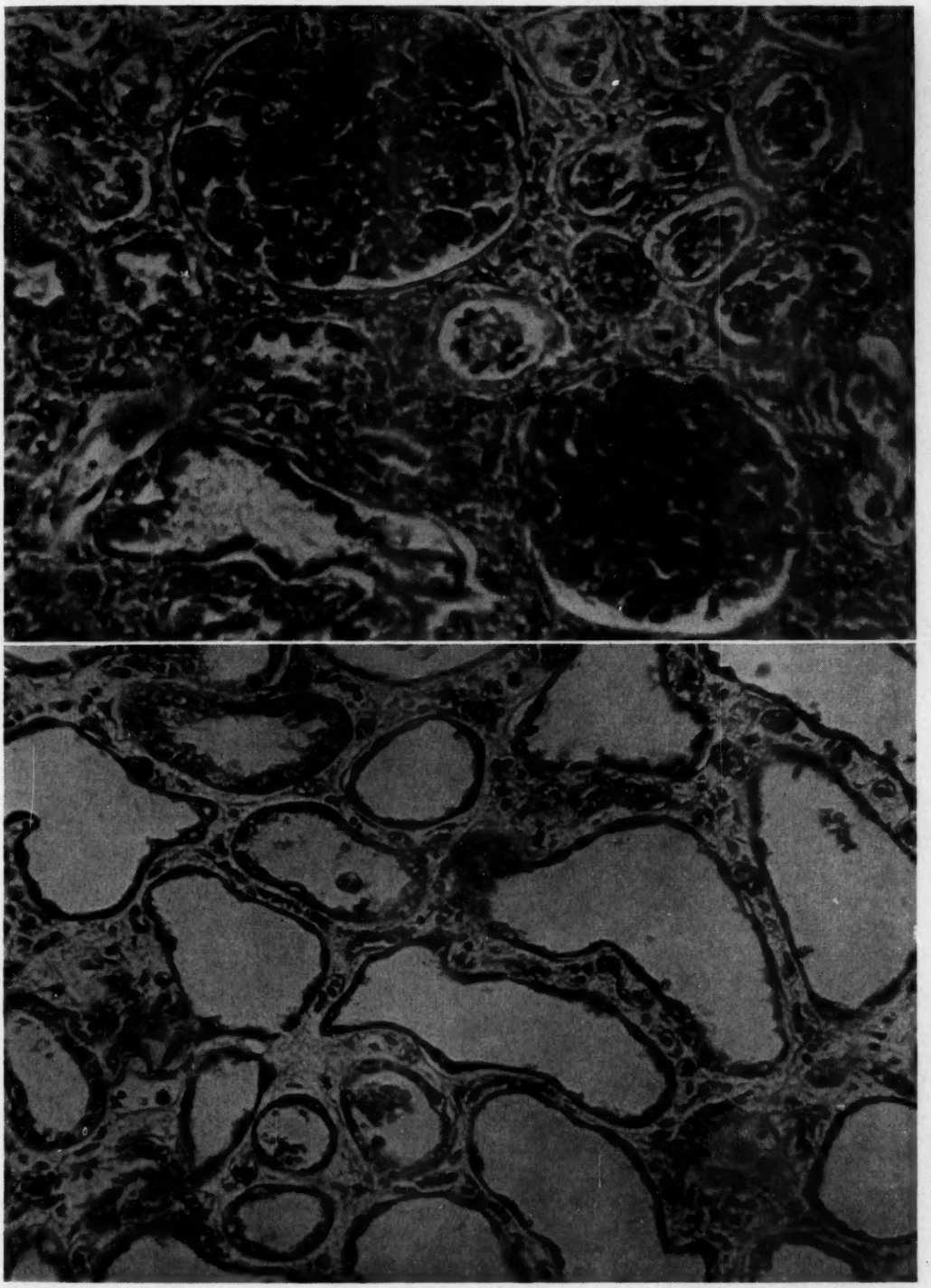


Fig. 2.

Fig. 1.—Case 1. Kidney showing hemorrhagic infarction of glomeruli.
Fig. 2.—Case 1. Kidney showing degeneration and necrosis of tubules.

During the procedure, while blood was being typed and cross-matched, the technician reported that the clot in the test tube dissolved completely within three minutes from the time it was drawn.

The patient's blood pressure remained 80/40, and it was necessary to use intravenous Expandex, whole blood, and vasoconstrictors to maintain this pressure. During the administration of 2,000 c.c. of whole blood after operation, clotting times were taken every fifteen minutes and within two hours the clotting time of the peripheral blood became normal and no lysis occurred. The blood pressure remained low, however, and intravenous adrenocortical extracts were given, but did not alter the clinical state.

At 3:30 P.M. (about four hours postoperatively), it was discovered that the patient's abdomen was distended and a diagnosis of intra-abdominal bleeding was made. She was taken to the operating room and the incision reopened. There was about 2,500 c.c. of fresh and clotted blood in the abdominal cavity. No bleeding vessels could be found, but all raw surfaces were oozing. Bleeding could not be controlled by ligating the ovarian and uterine vessels, or with bovine thrombin packing. The patient received 9 pints of blood during this procedure and was seen in consultation by a hematologist (at 5:30 P.M.) who made the diagnosis of hypofibrinogenemia due to excessive fibrinolytic substance in the circulating blood stream. Four grams of fibrinogen was then given and the clotting time came back to normal almost immediately and bleeding ceased.

The incision was closed after the patient had been on the operating table for one hour and fifty minutes. Her blood pressure at the end of operation was 120/80.

For forty-eight hours postoperatively, her condition appeared good, after which it began to deteriorate. The problem of maintaining the patient in electrolyte balance became a major issue. Daily determinations of blood chemistry and replacement of sodium, potassium, and chlorides intravenously were attempted with some success, but it was quite evident that the kidneys were shutting down. With the advent of a lower nephron syndrome, the nonprotein nitrogen and icteric index rose to over 200 and she became oliguric. Table I shows the abnormal chemical findings reported.

The patient was transferred to the Cleveland Clinic on April 21 and treated with the artificial kidney but she died on April 25.

A postmortem was done which showed "gross peritonitis and pelvic abscesses, suppuration with many abscesses in both kidneys. There was some pancreatic fat necrosis around the pancreas but no serious pancreatitis. The liver was yellow, necrosis could not be seen grossly." The kidneys were examined and the pathologist's microscopic findings were as follows: the glomeruli were well preserved with some capillary congestion; the tubules were dilated, some showing marked vacuolation; brown homogeneous casts were seen in many of the tubules; in others there were albuminoid casts; masses of polymorphonuclear leukocytes were seen in some tubules. In some areas there were large wedge-shaped, hemorrhagic infarctions involving glomeruli, tubules, and vessels. In these areas there was marked congestion of glomeruli and arterioles.

The cause of death was kidney failure (lower nephrone syndrome) due to shock which resulted from uncontrollable hemorrhage secondary to hypofibrinogenemia.

TABLE I. ABNORMAL CHEMISTRY DETERMINATIONS WHILE PATIENT E. M. WAS AT MT. SINAI HOSPITAL

	APRIL									
	12	13	14	15	16	17	18	19	20	21
Nonprotein nitrogen (mg./100 ml.)	41.0			60.0		116.0		153.0	200.0	205.0
Icteric index			117.0					230.0	222.0	
Creatinine N. (mg./%)						14.3		16.8	19.0	19.6
CO_2 (Vol. %)	35.3		31.5	27.7	24	24.0		18.2	18.3	12.6
Bilirubin 1 minute (direct) (mg./100 ml.)			12.04	15.5				25.3		
Total (mg./100 ml.)			21.5	28.2				41.0		
Urine output (c.c.)		860	570.0	500.0	250	(Urine mixed with liquid stools)				

CASE 2.—T. C., a 39-year-old Negro woman, para ii, gravida iii, whose expected date of confinement was Jan. 22, 1954, was admitted at 1:40 P.M. on Jan. 13, 1954, in early labor. At 5:45 P.M. (four hours after admission), she was given 100 mg. Demerol and 3 grains Seconal intramuscularly. (Hykinone, 1 c.c., was given on admission.) Labor continued satisfactorily up to 7:30 P.M. when vaginal bleeding was first noticed. Fetal heart tones were not recorded after admission and on the nurses' notes at 9 and 10 P.M. they were questionable. At 11:08 (about ten hours after admission), the patient was delivered of a 9 pound 6 ounce stillborn female infant with great difficulty under 50 mg. procaine spinal anesthesia. She went into shock immediately after the anesthetic was given and started to bleed profusely without clots immediately after delivery of the placenta. The blood pressure remained at 70/40 in spite of vasoconstrictor drugs, Pitocin, and blood transfusions and the hemorrhage continued. At this time the hemoglobin determination was 5 Gm. per 100 ml. of blood and patient received 1,600 ml. whole blood and 4 Gm. of fibrinogen, but the blood would not clot and the pressure remained at shock level. She died at 4 A.M. on Jan. 14, 1954 (five hours after delivery).

A postmortem was done. There was 400 c.c. of unclotted blood in the peritoneal cavity. Blood taken from the left ventricle failed to clot even with the addition of thrombin. The lungs failed to show squames. The kidneys were normal.

The impression was: afibrinogenemia due to premature separation of the placenta (and shock) with excessive fibrinolytic substance in the circulating blood stream.

CASE 3.—J. R., a 22-year-old white woman, para 0, gravida i, was admitted on Dec. 27, 1954, at 1:20 P.M. in early labor.

She was seen by her obstetrician for the first time on Nov. 18, 1954 (one month prior to her admission), stating that she had been under obstetrical care out of town and had a very normal prenatal course. At the first office visit, the pregnancy was verified, but fetal heart tones could not be heard, although a loud souffle over the entire uterus was quite audible. The size of the uterus at this time was that of about a 6 to 6½ months' pregnancy and did not correspond to her expected date of confinement which was to be Feb. 26, 1955, as figured from her last normal period May 19, 1954.

The patient returned to the office on Dec. 9, 1954 (three weeks later), and the fetal heart was still not heard. An x-ray was taken and the report stated that there was no evidence of fetal death.

After admission to the labor suite, the patient was given 1 c.c. Hykinone, 100 mg. Demerol, 1/150 grain scopolamine, and 50 mg. Seconal. At 3:45 P.M. (two hours and forty-five minutes after admission) she aborted a macerated fetus spontaneously without anesthesia or surgical intervention. At 4 P.M. (fifteen minutes later), the patient began to bleed profusely, without clots, and the bleeding could not be controlled with Pitocin. She was taken to the operating room for vaginal examination, and uterine packing with whole blood running. Consultation was also obtained from a hematologist who verified the tentative diagnosis of hypofibrinogenemia on peripheral blood and gave the patient 4 Gm. of fibrinogen intravenously. The bleeding ceased immediately and clotting became normal.

The patient made an uneventful recovery and was discharged Jan. 4, 1955, apparently cured.

Summary

Hypofibrinogenemia as a cause of postpartum hemorrhage is a definite entity. It should be suspected in cases of premature separation of the placenta, dead fetus, and shock associated with hemorrhage. Diagnosis should be made as quickly as possible and treatment with human fibrinogen and whole blood instituted promptly. In cases of excessive lytic substance in the blood, more investigation is needed. It is suggested that toluidine blue may be used to neutralize the fibrinolytic substance.

Hypofibrinogenemia (afibrinogenemia) has been discussed and three diagnosed cases of postpartum hemorrhage due to depletion of fibrinogen from the circulatory blood stream have been reported with two maternal deaths resulting.

In Case 1, the condition was not suspected and the patient, E. M., died two weeks after delivery, possibly from kidney damage due to an irreversible lower nephron syndrome.

The second patient (T. C.) died of hemorrhage and afibrinogenemia due to an excessive amount of circulatory fibrinolytic substance.

The third patient (J. R.) lived because of the quick diagnosis and rapid therapy with fibrinogen (about forty-five minutes from onset).

Acknowledgment is made to Drs. O. Ratnoff and L. Goldberg for their cooperation and to Dr. V. Woldman for permitting the use of Case 2.

References

1. Coon, Hodgson: Surg., Gynec. & Obst. **95**: 717, 1952.
2. Chassin, H., and Grennwald, C.: J. Mt. Sinai Hosp. (N. Y.) **20**: 4, 1953.
3. Dieckmann, William J., and Daily, Edwin F.: Am. J. Obst. & Gynec. **30**: 1, 1935.
4. Gitlin, D., and Borges, W. H.: Blood **8**: 8, 1953.
5. Maisel, F. J., Cartnick, E. N., and Zaino, E. C.: Obst. & Gynec. **3**: 204, 1954.
6. Moldavsky, L. F., Crowley, J. H., and Hesselbrock, W. B.: Ohio M. J. **49**: 111, 1953.
7. Hildago, J., Fowell, A. H., and Ralls, R. J.: Surg., Gynec. & Obst. **95**: 661, 1952.
8. Peckham, C. H., Jr., and Middlebrook, L. F., Jr.: Am. J. Obst. & Gynec. **65**: 644, 1953.
9. Ratnoff, O. D., Lanster, C. F., Sholl, J. G., and Schilling, M. O.: Am. J. Med. **13**: 111, 1952.
10. Ratnoff, O. D., and Vosburgh, G. J.: New England J. Med. **247**: 970, 1952.
11. Reid, D. E., Weiner, A. E., and Diamond, L. K.: Am. J. Obst. & Gynec. **66**: 500, 1953.
12. Reid, D. E., Weiner, A. E., and Roby, C. C.: Am. J. Obst. & Gynec. **66**: 465, 1953.
13. Ratnoff, O. D.: Hemorrhagic States During Pregnancy, presented before the Division of Obst. & Gynec., Mt. Sinai Hospital, Cleveland, Ohio, Jan. 16, 1954.
14. Weiner, A. E., Reid, D. E., and Roby, C. C.: Am. J. Obst. & Gynec. **60**: 379, 1950.

USE OF FEMALE SEX HORMONE THERAPY IN PREGNANT DIABETIC PATIENTS*

PRISCILLA WHITE, M.D., LUKE GILLESPIE, M.D., AND LLOYD SEXTON, M.D.,
BOSTON, MASS.

(From the Joslin Clinic)

THE inescapable conclusion that female sex hormone therapy gives added maternal and fetal protection when pregnancy complicates diabetes mellitus is based upon experience with more than 1,100 cases of diabetic pregnancies treated in the Joslin Clinic for over half a century. Among these 1,100 cases, assays for one or more of the female sex hormones of pregnancy have been determined in 780 viable pregnancies (completion of 28 weeks).

The Problem

The essentially malignant combination of pregnancy and diabetes was shown decisively in the pre-insulin era when the few diabetic women who conceived rarely survived pregnancy. The harmful effects of diabetes upon fetal survival were shown just as decisively in the early insulin era when spontaneous abortion, ante- and intrapartum and neonatal deaths occurred in more than one-half of these cases.[1]

Possible Causes for Failures.—In the search for the cause and the means of preventing these accidents, their correlation with poor chemical control of diabetes has been a natural one.[2-6] Ketoacidosis, especially occurring in the second trimester, is almost invariably lethal; but, in our experience, early and late fetal losses occur without the slightest evidence of diabetic acidosis, and good chemical control of diabetes does not guarantee fetal survival. The difference in chemical control of diabetes as measured by the degree of hyperglycemia in mothers of surviving and nonsurviving infants has been so slight that we have sought elsewhere for the cause of fetal deaths. Our cases of diabetic pregnancy studied prior to the year 1940 showed normal average postprandial blood sugar levels for the entire period of the third trimester whether the infant survived or not. Thus the average postprandial blood sugar level of mothers of the infants who survived was 145 mg. and of those whose infants did not survive, 156 mg.

With the recognition of the placenta as an important endocrine gland, disturbances of its hormonal regulation and production have been correlated with the problems found in diabetic pregnancies. Studies to investigate possible disturbances in the metabolism of cortisone[7] and related adrenocortical steroids have shown no differences between diabetic women who have normal

*Presented at the joint meeting of the Chicago Gynecological Society, the Chicago Pediatric Society, and the Chicago Diabetic Association, Nov. 19, 1954.

or abnormal pregnancies or in nondiabetic women whose pregnancies were normal or abnormal. An imbalance of female sex hormones—low levels for serum estrogen, low levels for progesterone as measured by pregnanediol excretion, and high levels for chorionic gonadotrophin[1, 8, 9] has been the common hormonal pattern.

Five Contended Points

It has been the claim of Smith and Smith[8] and of our group: (1) that this imbalance occurs in abnormal pregnancies in diabetic patients, (2) that it predicts or precedes the complications of pregnancy, (3) that it can be corrected by the administration of female sex hormones, (4) that such correction is followed by improved fetal survival provided other parts of management of pregnancy and diabetes are observed, and (5) that the imbalance occurs more often and to a greater degree as the evidence of maternal vascular damage increases. All these points have been contended. For this reason in 1954 we planned to retest nondiabetic controls. In July, 1954, the results of the obstetrical diabetic program of the British Medical Research Council were presented in America by Mr. Charles Gray.[7] These results confirmed in part, but only in part, our earlier observations, namely, that the abnormal pattern of female sex hormones exists in diabetic pregnancy, that it precedes the accidents of pregnancy, and that it can be corrected by sex endocrine therapy. Our most important contention, that correction alters survival, was most certainly not confirmed. In their study of alternate cases treated with and without oral stilbestrol and oral ethisterone or placebos, cases with retinopathy were excluded; therefore the correlation with vascular damage was not reported.

A Classification of Cases in This Study Seems Essential. Although the classification used in our patients[3, 5, 10] has been published many times, its details still appear confusing.[5] It is reviewed here briefly to indicate its purpose and its value. This classification of casses was designed to separate benign from malignant forms of diabetes, to separate patients with and without vascular disease. It has pointed out benign cases of diabetes in which pregnancy is more diabetogenic than it is in malignant cases. It has indicated malignant cases in which pregnancy may precipitate vascular lesions or accelerate existing ones. It has indicated the trend of fetal mortality and has suggested different programs for management of cases and for timing of delivery. Thus Class A consists of subclinical cases of diabetes (non-insulin users); Class B, the more benign type of diabetes in which onset occurs in adult life and which is short in duration so that vascular damage is improbable, and those patients in whom clinical evidence of vascular damage has not been found; Class C, near non-insulin producers without vascular damage or those cases where vascular damage may be latent because of the duration of the disorder; Class D, total or near total diabetes or cases where vascular damage is probable because of duration of diabetes, or those which show retinitis or calcified leg arteries; Class E, those which show vascular involvement in the pelvis; and Class F, those with intercapillary glomerulosclerosis. (The

relative fetal survival rates in the 278 cases treated without female sex hormone therapy for the entire period of pregnancy, Classes A to E, are, respectively, 100, 67, 48, 32, and 13 per cent [Table I].)

TABLE I. CLASSIFICATION OF DIABETIC PATIENTS AS TO RISK OF PREGNANCY

Class A—Diabetes shown by glucose tolerance test
Class B—Diabetes with onset after age 20, duration 0-9 years, and no vascular disease
Class C—Diabetes with onset between ages of 10 and 19, duration 10-19 years, and no vascular disease
Class D—Diabetes with onset before age 10, duration 20+ years, and vascular disease evidenced by calcification of leg arteries and retinopathy
Class E—Diabetes with calcified pelvic arteries
Class F—Diabetes with nephropathy

Evidence Supporting the Five Contended Points.—To determine whether or not an abnormal pattern of female sex hormones occurred in abnormal diabetic pregnancies, three such groups were selected for comparison with those cases of diabetes in which the course was normal and the infant survived.

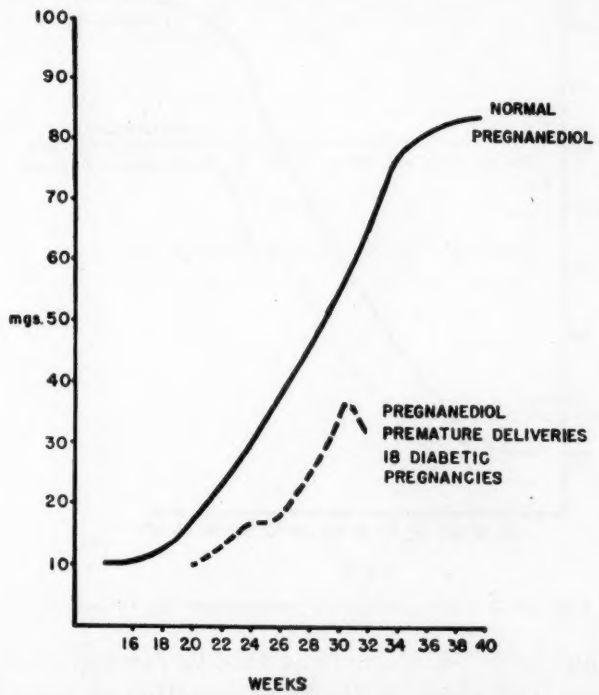


Fig. 1.—Spontaneous premature delivery. Eighteen pregnancies terminating before the thirty-fourth week.

These three groups were: (1) patients who had premature spontaneous deliveries before the thirty-fourth week, (2) patients who had pre-eclampsia so classified by the obstetricians, and (3) patients who had intrauterine or neonatal fetal deaths. Median pregnanediol curves were plotted for all cases in which six or more pregnanediol determinations had ben made between the twentieth and the thirty-second weeks, averaging a determination every two weeks. These curves were then compared with the normal curve published

by Venning,[11] used in our laboratory as the normal. The lowest excretion of pregnanediol with the greatest deviation from the average normal was found among the spontaneous premature deliveries. The average excretion in 18 cases shown in Fig. 1 deviates from the normal from week 20 with a moderate drop at week 24 and a marked fall at week 30. The curve for 24 cases complicated by toxemia deviates from the normal from week 18 with a break again at week 30 (Fig. 2). In 44 cases in which the infants were lost, the average curve deviated from the normal, which it followed closely until week 24, and showed a second break at week 32 and a plateau at week 33 (Fig. 3). In contrast, the curve for 173 diabetic patients with a normal course and successful outcome can be superimposed upon the normal until week 28, when it falls below normal but the difference is very slight (Fig. 4).

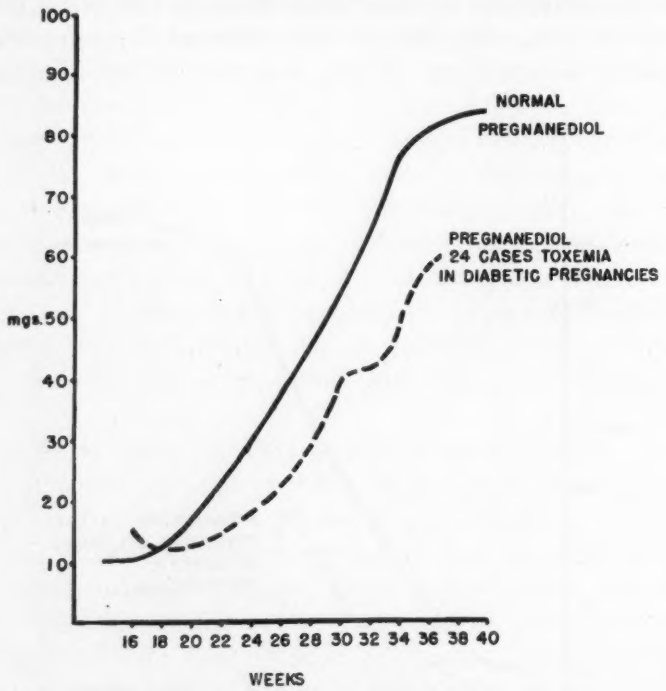


Fig. 2.—Twenty-four cases complicated by toxemia.

Evidence of the correction of the imbalance by female sex hormone therapy and its importance: The effect of the administration of female sex hormone therapy upon changes in hormone levels and the significance of the changes were evaluated by a comparison of all cases which showed an imbalance of female sex hormones—either the fall of pregnanediol or the rise of chorionic gonadotrophin or both. These abnormal cases were divided into three groups: abnormal untreated; abnormal treated with female sex hormone therapy which exhibited no chemical response to the therapy; and, finally, those cases which were treated with female sex hormone therapy which did respond by a change in serum chorionic gonadotrophin or urinary pregnanediol level. The comparison was made by Dr. Joselyn Rogers[12] from the Department of Obstetrics

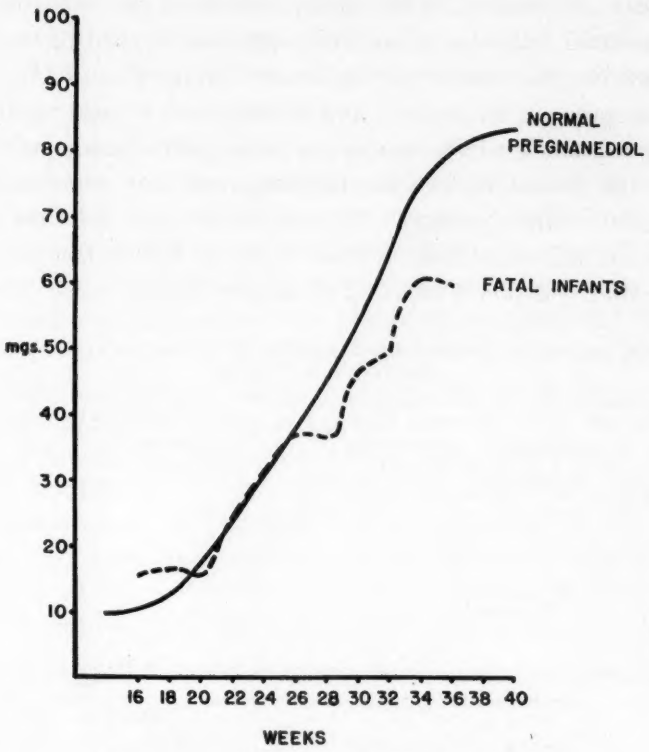


Fig. 3.—Infants lost. Forty-four cases.

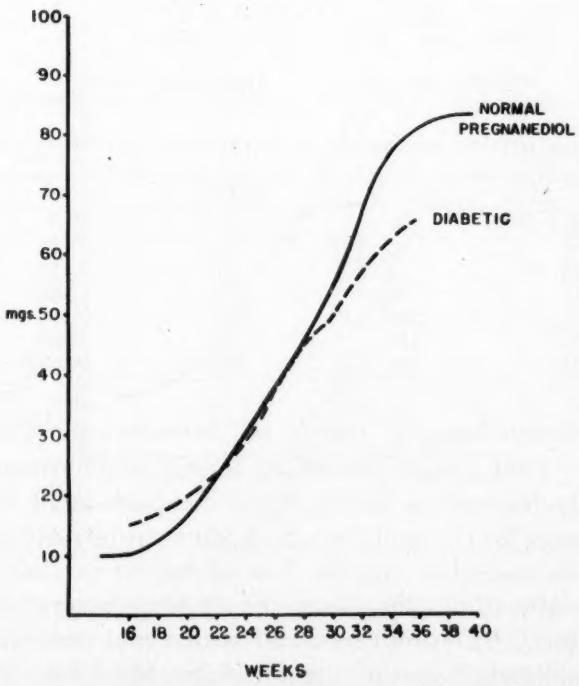


Fig. 4.—Liveborn and surviving infants in pregnancies uncomplicated by premature delivery (before the thirty-fourth week) or by toxemia (173 cases).

at the University of Toronto. The clinical course of the patients in these three groups and the fetal outcome were then compared according to our Classifications A through F (the results are shown in Tables II and III). The clinical course was the same in untreated and unresponsive cases and, although the clinical course was not entirely normal in those patients who showed the chemical response, the incidence of complications was low compared with the incidence in the two other groups. Although the fetal salvage was somewhat higher in treated unresponsive patients than in the untreated, it fell below that of the treated responsive cases of all of our classes except B.

TABLE II. CORRELATION OF LABORATORY RESPONSE TO HORMONE THERAPY AND ABNORMAL OBSTETRICAL COURSE

CLASS	ABNORMAL UNTREATED % (PER CLASS)	ABNORMAL TREATED (A) NO RESPONSE % (PER CLASS)	ABNORMAL TREATED (B) WITH RESPONSE % (PER CLASS)
A			
B	66	45	33
C	68	70	28
D	75	73	43
E		85	43
F	Insufficient cases		

TABLE III. CORRELATION OF LABORATORY RESPONSE TO HORMONE THERAPY AND FETAL LOSS

CLASS	ABNORMAL UNTREATED % (PER CLASS)	ABNORMAL TREATED (A) NO RESPONSE % (PER CLASS)	ABNORMAL TREATED (B) WITH RESPONSE % (PER CLASS)
A		7	13
B	20	13	1
C	25	17	7
D	46	62	29
E			
F	Insufficient cases	Insufficient cases	Insufficient cases

TABLE IV. DAILY INTRAMUSCULAR DOSAGE OF STILBESTROL AND PROLUTON (IN MILLIGRAMS)

WEEK OF PREGNANCY	CLASS B	C	D	E	F
0-16	25	25	25	25	25
17-19	25	25	50	50	50
20-23	50	50	100	100	100
24-29	100	100	125	125	125
30-33	100	100	150	150	150
34 to end	125	125	200	200-250	200-250

Evidence that imbalance of female sex hormones parallels the degree of vascular damage: That the imbalance of female sex hormones parallels the degree of vascular damage is shown by a comparison of the pregnanediol excretion for Classes B, C, and D, which show progressively low excretion levels (Fig. 5). Our schedule for the dose of female sex hormones varies according to our classification—the progressively more severe classes receiving a higher dose schedule. The program consists of equal doses of stilbestrol and progesterone administered as an intramuscular injection (Table IV). The treatment which is given to the patients at the diagnosis of pregnancy is reg-

ulated by their subsequent chemical and clinical responses: Classes B and C progressing from 25 mg. to 125 mg., Classes D, E, and F, from 25 mg. to 250 mg., but if the chemical tests or clinical progress are abnormal the schedule is advanced to the next four-week period.

Effect of female sex hormone therapy upon early and late fetal salvage: The immediate objective of our therapeutic program has been to increase the fetal salvage. The over-all survival in the 628 cases of viable pregnancies which completed the twenty-eighth week, studied and treated since 1938, can be compared with the survival in 48 cases in which the assays showed normal levels and in 104 cases in which the assays were classified as abnormal (Tables V and VI). The survival in those with normal hormone levels was 96 per cent. In those cases in which abnormal curves occurred but no therapy was given, the survival was only 54 per cent, and in the 628 treated cases the survival was 89 per cent. Since therapy in this latter group was started prior to the demonstration of the imbalance, a fairer comparison might be made between the total 152 untreated cases and the 628 treated cases (Table VI). The former showed a fetal and infant survival of but 68 per cent and the latter 89 per cent. The review of our assays indicates to us that not more than 5 per cent were treated without chemical indication for the therapy.

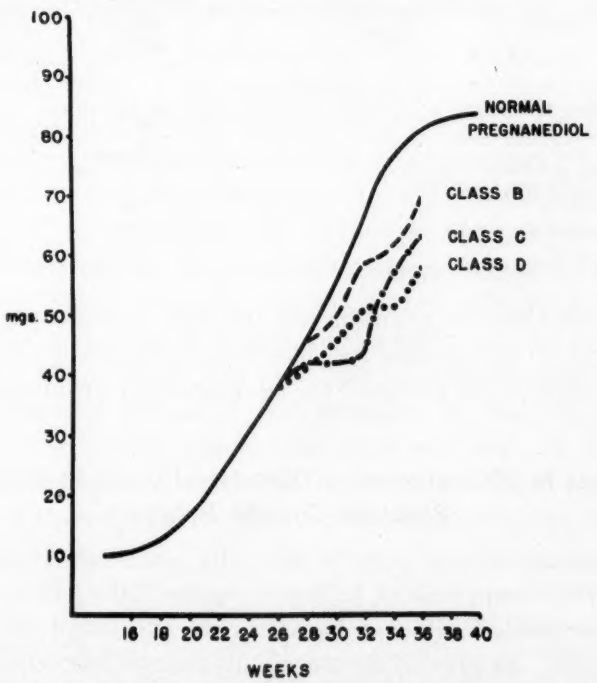


Fig. 5.—Pregnanediol excretion in diabetic pregnancies by class compared with the normal.

With the passage of time, it has been difficult to improve fetal salvage. Long-acting insulins, chemotherapy, and antibiotics available since 1935 have changed the character of the diabetic population so that by our classification more and more of our obstetrical patients fall into Classes D, E, and F, where

the chances for fetal mortality and maternal morbidity increase. Nearly half, 47 per cent, of our 313 treated cases delivered at the Boston Lying-in Hospital since Aug. 1, 1950, and studied up to Nov. 8, 1954, fall into Classes D, E, and F, and only 25 per cent into Classes A and B. Contrast this with our experience prior to the year 1940; only 12 per cent were in Classes D, E, and F; in fact there were none in E and F, and 55 per cent in Classes A and B. The distribution of fetal loss by duration of pregnancy in the 313 recently treated cases (Table VII) indicates that the losses under week 16 and from week 16 to week 28 are low. Our 13 per cent loss of viable infants after week 28 in our 313 recently treated cases constitutes our main problem.

TABLE V. FETAL SURVIVAL. ALL CASES STUDIED

	NUMBER	SURVIVAL (%)
Total cases	780	84
Abnormal:		
Untreated	104	54
Treated	628	89
Normal	48	96

TABLE VI. FETAL SURVIVAL. TREATED AND UNTREATED CASES

	NUMBER	SURVIVAL (%)
Total untreated	152	68
Treated	628	89

TABLE VII. DISTRIBUTION OF FETAL LOSS BY DURATION OF PREGNANCY IN 313 TREATED CASES

	NUMBER	%
Spontaneous abortion	15	5
Previable	12	4
Intrauterine death	10	3
Neonatal	28	9

It thus seems that our spontaneous abortion rate compares favorably with that of the general population as does the incidence of toxemia, which fell from the high level of 33 per cent in the untreated group to 3 per cent in the treated group.

Differences in Management of Obstetrical Cases in British Medical Research Council Program

The comparison of our results with the challenging ones of the British Medical Research Council is as follows: Some 150 of their cases of diabetic pregnancy were treated alternately with oral stilbestrol and oral ethisterone and with placebos. As previously stated, all cases with retinitis were excluded. The groups were well matched and would be classified as A, B, and C. The fetal survival in treated and untreated cases after the twenty-eighth week was 70 per cent and 68 per cent, respectively. The corresponding survival in 249 of our cases of viable pregnancy treated since August, 1950, which showed no retinopathy was 91 per cent (Table VIII). The differences in management consist of: first, the type of therapy employed, second, the quan-

tity used; third, the route of administration; and fourth, their rigid program irrespective of class, clinical or chemical course. Perhaps the most important reason why their fetal mortality was so high for obstetrical patients with a mild type of diabetes was the lack of individual and constant care and attention. The conditions necessary for an alternate-case type of experiment prevent the applicatin of the principle of individualization of management, so important in the entire practice of medicine.

TABLE VIII. TOTAL AND VIABLE FETAL AND INFANT SURVIVAL IN 249* CASES WITHOUT RETINITIS

Viable pregnancies		230
Spontaneous abortion	10	
Premature delivery	11	
Stillborn	4	
Neonatal death	17	
	42	
Total fetal survival		84%
Total fetal survival in patients without retinitis		91%

*Of 313 patients, 64 had retinitis.

Our selection of parenteral rather than oral therapy has been based on the poor fetal survival which has occurred in our patients who received the oral type of medications. Failure in absorption of oral medication is believed to account for the difference. Poor absorption often occurs in diabetes because of the high incidence of gastrointestinal neuropathies and poor absorption is accepted as one of the physiological changes of pregnancy. A theoretical difference exists, too; in parenteral therapy the unconjugated hormones become available whereas in oral therapy the hormones are conjugated almost immediately. In addition to the fetal salvage other differences in relation to the infant have been observed; thus the weight, though still greater than the average normal for the period of gestation, is markedly less in treated than it is in untreated cases. Reports of fetal pathological examinations show that those findings which formerly indicated the presence of diabetes in the mother, namely, hepatomegaly, and erythropoiesis,[13] are not observed in these infants, and the placenta[14] which formerly the pathologists could identify as being characteristic of diabetes, hypertension, or nephritis is reported to be normal for the period of gestation.

Other Effects

Certain interesting and important side reactions have been observed in relation to the diabetic mother. To the student of diabetes, pregnancy is but an episode and these after-effects concern us even more. The three most significant findings are: (1) the probable effect of this management upon the course of retinopathies, (2) the possible protection against nephropathies, and the future development of coronary heart disease, and (3) the most exciting probable effect, that upon the course of diabetes itself.

In 1949 and 1950, Dr. William P. Beetham[15] reviewed the retinopathies in our obstetrical diabetic patients and warned us that severe retinopathies were progressing during pregnancy and that some of these were not being reversed with the termination of pregnancy. Since the fetal salvage in these patients (Table IX) with advanced retinitis and especially retinitis proliferans was poor, he suggested that therapeutic abortion was indicated. Our Catholic patients, however, refused our medical advice. A revision of therapy was attempted in order to give these patients increased protection. The only part of our schedule which we thought could be revised was the dose of female sex hormones, so at this time the therapy was altered, especially for patients in Classes D, E, and F. In the past two years Dr. Beetham has reported to us that patients with severe retinitis end their pregnancies with no progression of the retinopathy, and that sometimes, to his surprise, the eyes appear in even better condition at the end of pregnancy than they were at the start. This statement, of course, refers only to those patients with nonproliferating retinitis. Formation of new blood vessels and fibrous scars have not been changed. The possible protection against progression of intercapillary glomerulosclerosis is suggested because clinical and pathological evidence favors the similarity of these complications.

TABLE IX. RETINITIS AND FETAL SURVIVAL

	NUMBER	TOTAL FETAL SURVIVAL (%)
Nonproliferating Retinitis.—		
Treated with female sex hormones	57	70
Treated without female sex hormones	16	16
Proliferating Retinitis.—		
Treated with female sex hormones	7	57
Treated without female sex hormones	14	0

Possible protection also against the future development of coronary heart disease in this group is suggested by the work of Ruth Pick,[16] who has found that estrogenic substances protect the coronary arteries. Since the incidence of this disease is high among diabetic women, this group is under close observation for clinical signs of the presence or absence of coronary artery disease.

The most exciting effect observed in these patients appears to be upon the course of diabetes. In a significant number but not all of these patients, some six months after delivery, severe insulin hypoglycemia occurred. It was necessary for these patients to reduce an average dose of insulin—40, 50, and 60 units—to 10 or 15 units and such small doses of insulin have controlled their diabetes adequately for as long as 10 years—the longest time any of them has been under observation. A statistical evaluation of these cases was made. Insulin trend curves, the ratio of insulin to body weight, were plotted up to the time of delivery. Predicted curves were extrapolated beyond delivery. Patients fell into two groups: those in whom the insulin trend curve was rising spontaneously and those in whom the insulin curve was falling spontaneously. Whether the trend was increasing or decreasing, it was altered in a significant

number of these patients in a significant degree following delivery and following the management outlined. The greatest number of improved cases occurred where the trend was increasing. This experience appears to be similar to that reported in experimental diabetes by Houssay and associates.[17, 18] He found estrogenic substances caused islet hypertrophy and hyperplasia. Pathological examination of the pancreas in one of our long-term juvenile cases in this series revealed hypertrophy and hyperplasia of pancreatic islets, never reported in any patient with long-term juvenile diabetes. Such observations suggest possible programs for protection against retinopathy, nephropathy, and coronary heart disease, as well as possible methods for attempts to alter the course of diabetes in our nonpregnant diabetic patients.

Total Treatment

Our total treatment consists of seven parts: (1) classification of patients, (2) chemical control of diabetes, (3) female sex hormone therapy, (4) measures used to prevent or correct edema and especially hydramnios, (5) early timing of delivery, (6) special care of the infant in the immediate postnatal period, and (7) yearly observation of the offspring of the diabetic mother for evidence, clinical or chemical, of the disorder, diabetes. Female sex hormone therapy, therefore, is but one seventh part of our entire program and the other six parts cannot be ignored. Thus if diabetic coma occurs in the second trimester in patients who are receiving female sex hormones, the infant may die. Edema and hydramnios occur among these patients treated with female sex hormones although we think it occurs later and to a lesser degree. Low-sodium, high-protein diets, ammonium chloride and mercury compounds, and even transabdominal amniotomy are employed. Early timing of the delivery remains an important part of the program. With female sex hormone therapy, however, more of these infants reach viability, the incidence and harmful influence of toxemia and prematurity being lessened. Although the vascular pattern of the placenta in the treated case appears to be normal, the entire vascular system, arteries, capillaries, veins, and venules of the pelvis of the diabetic woman, is not normal. It is difficult to estimate at what period the vascular system of her generative organs will fail. Therefore, we still deliver those patients with demonstrable vascular damage at the end of the thirty-fifth week but postpone delivery in uncomplicated cases of diabetes to the thirty-seventh week if possible.

The need for special care of the infant must still be emphasized. These infants are premature, often delivered by cesarean section, two factors which favor the development of the pathological condition which appears significant in them, namely, the hyaline membrane syndrome with resorption atelectasis. In addition to prematurity and delivery by cesarean section, it is our belief that diabetes itself predisposes to this condition.

Most important of all, it is still necessary to protect the offspring against diabetes, but the need is no greater in the infant of the diabetic mother than it is in the offspring of the diabetic father (Table X).

In our experience, female sex hormone therapy added to the six other principles of management appears to give greater fetal and maternal protection.

TABLE X. INCIDENCE OF CLINICAL AND CHEMICAL DIABETES IN CHILDREN OF YOUNG DIABETIC PARENTS

DIABETIC	CHILDREN (NO.)	CLINICAL DIABETES (%)	CHEMICAL DIABETES (%)	COMBINED (%)
Father	85	9	12	21
Mother	100	9	14	23
Father and mother	19	32	30	62

References

1. White, P.: Am. J. Med. 7: 609, 1949.
2. Reis, R. A., DeCosta, E. J., and Allweiss, M. D.: AM. J. OBST. & GYNEC. 60: 1023, 1950.
3. Jones, W. S.: AM. J. OBST. & GYNEC. 66: 322, 1953.
4. Long, N. W., Hartmann, W. L., Futcher, P. H., and Eastman, N. J.: Obst. & Gynec. 3: 160, 1954.
5. Pedersen, Jorgen: Diabetes 3: 199, 1954.
6. Eastman, N. J.: Obst. & Gynec. Surv. 1: 1, 1946.
7. Gray, Charles: Personal communication.
8. Smith, G. V., and Smith, O. W.: West. J. Surg. 55: 288, 1947.
9. White, P., and Hunt, H.: J. A. M. A. 115: 2039, 1940.
10. Given, W. P., Douglas, R. Gordon, and Tolstoi, E.: AM. J. OBST. & GYNEC. 59: 729, 1950.
11. Venning, E. M.: J. Biol. Chem. 119: 473, 1937.
12. Joslin, E. P., Root, H. F., White, P., and Marble, A.: The Treatment of Diabetes Mellitus, ed. 9, Philadelphia, 1952, Lea & Febiger, chap. 27, p. 686.
13. Joslin, E. P., Root, H. F., White, P., and Marble, A.: The Treatment of Diabetes Mellitus, ed. 9, Philadelphia, 1952, Lea & Febiger, chap. 27, p. 695.
14. Ober, William: Personal communication.
15. Beetham, W. P.: Diabetic Retinopathy in Pregnancy, Tr. Am. Ophth. Soc., vol. XLVIII.
16. Pick, Ruth: Personal communication.
17. Houssay, Bernardo A.: Brit. M. J. 2: 505, 1951.
18. Houssay, B. A., Rodriquez, R. R., and Cardeza, A. P.: Endocrinology 54: 550, 1954.

81 BAY STATE ROAD

Discussion

DR. RALPH R. REIS.—The diabetic woman owes two real debts of gratitude. The first is for the discovery of insulin which has helped her not only to survive but also to mature and to bear children. The second debt is for the work of the many who have done so much to make these processes safe and satisfactory for both mother and child.

Dr. White has labored long and well in the field of diabetes and pregnancy. Her excellent results, first published in 1935, have continued throughout the years and have resulted in the salvage of an untold number of mothers and babies. She has taught us many of the principles of the management of diabetes and pregnancy. These include: (1) careful evaluation of the diabetic woman *before* pregnancy, (2) a fine practical, working classification of diabetic women, (3) meticulous and continuing almost constant diabetic management throughout pregnancy, labor, and the puerperium, and (4) early termination of pregnancy as a means of increasing fetal salvage and avoiding the dangers of diabetic postmaturity. Finally, we have just been privileged to hear her results by the use of hormones in the management of the pregnant diabetic patient.

Careful evaluation of the cardiovascular renal system of the diabetic woman should be done *before* pregnancy. The amount of premature vascular sclerotic changes must be determined by evaluation of kidney function, blood pressure levels, eye ground examinations, and x-ray study of the iliac vessels. Such a program will help to differentiate between

premature vascular aging and true toxemia of pregnancy. It probably helps to account in part for the low incidence of toxemia of pregnancy in our own patients. We are of the opinion that hypertension, proteinuria, and edema in pregnancy do not always mean toxemia of pregnancy.

The meticulous management which Dr. White has taught us includes constant and continuing diabetic control. We now know that these patients must be seen once or twice a week throughout pregnancy, must be hospitalized for primary control occasionally during pregnancy and always for some time before termination of pregnancy. Such control is carried out by the joint care of the internist and the obstetrician and not by independent management. It is most important during the first and third trimesters and particularly during labor and the puerperium. There is some difference of opinion as to the aims of diabetic management during these periods. These, I am not qualified to discuss. Suffice it to say that we have achieved our best results by stabilization of carbohydrate metabolism at a level which will prevent symptoms, achieve and maintain normal body weight, develop a "sense of well being" and avoid acidosis, coma, and hyperinsulinism. Usually this means a continuing blood sugar level of 140 mg. per cent and a glycosuria of 10 to 15 Gm. per twenty-four hours.

Dr. White has taught us to terminate pregnancy early, during the thirty-fifth, thirty-sixth, or thirty-seventh week, thus increasing fetal salvage and avoiding diabetic postmaturity. An excellent criterion for the exact time is fetal weight and 3,500 grams has seemed to us to be the ideal weight.

The value of early termination is known now to all of us. It has been re-emphasized by a recent analysis of all published reports both in this country and in Britain showing that early termination resulted in a 60 per cent increase in fetal salvage in Britain and a 30 per cent increase in this country.

Tonight Dr. White has given her evaluation of hormone therapy. While I did not have the opportunity of reading her paper previously, I am privileged to know her position in this matter. Here we are in utter disagreement for it seems that the vogue of continuing and extensive hormone therapy is unwarranted on both theoretical and practical grounds. Hormone therapy is based on the investigation of the Smiths, which work in its entirety is confusing to most of us. Until the basic science laboratories give us accurate tests for hormone levels on which all can agree, such tests must remain equivocal and all work based on such tests must be questioned. In addition, there is still no proof that stilbestrol stimulates production of steroids by the placenta or that this would be desirable if it could be accomplished. Furthermore the results reported tonight by Dr. White are practically the same as she reported some 20 years ago without endocrine therapy.

Since no form of endocrine therapy yields better results than does the combination of careful diabetic management, good obstetric judgment, and meticulous pediatric care, no sex hormone therapy is used in our patients.

THE SIGNIFICANCE OF RENAL GLYCOSURIA IN PREGNANCY*

JEROME T. PAUL, M.D., CHICAGO, ILL.

RENAL glycosuria during pregnancy is significant for several reasons. The most important is its differentiation from true diabetes mellitus. Errors in diagnosis may be minimized if every patient showing glycosuria is considered to have diabetes until proved otherwise. It has been demonstrated that diabetes often begins during pregnancy and that pre-existing diabetes is often aggravated by pregnancy. In contrast to the diabetic, the pregnant woman with renal glycosuria is observed to have (1) normal blood sugar curves, (2) a small amount of sugar in the urine, and (3) lack of symptoms such as thirst and pruritus. Ultimately, the diagnosis of diabetes is established by the glucose tolerance test. It is necessary, however, to observe certain criteria in its interpretation. These include a fasting blood sugar level in excess of 130 mg. and a three-hour level above 120 mg.

Renal glycosuria occurs rather commonly in pregnancy. The incidence as reported varies. If glycosuria is limited to 100 mg. per cent or more, the frequency ranges between 5 and 35 per cent. Williams and Wills[1] detected glycosuria in 5.4 per cent of 640 pregnant women. Rowe, Gallivan, and Matthews,[2] in a series of thoroughly studied and well-controlled patients, found that 35 per cent showed sugar at some time during the antepartum period. In a recent study of 540 cases Batilwalla[3] found the incidence of glycosuria rose from about 5 per cent during the third month of pregnancy to about 40 per cent during the ninth month. The increased incidence of glycosuria during the second and third trimesters of pregnancy has been reported by other investigators.[4] It has been noted that glycosuria disappears abruptly after delivery. Usually no urinary glucose is found on the eighth day after delivery.

Glycosuria in pregnancy was observed over 100 years ago. Since then its causation has been ascribed to many factors. It may be partly explained by a lowering of the renal threshold for glucose. The lowered renal threshold is due to the diminished capacity of the epithelium of the proximal convoluted tubules to reabsorb sugar. It has been postulated that a deficiency of tissue phosphatase may be the abnormality producing consequent interference with the phosphorylation mechanism in the renal tubules on which sugar reabsorption depends. When tubular function is impaired the reabsorptive capacity of the tubules may be so reduced that dextrose will appear in the urine even at normal or low blood sugar levels. During pregnancy the average renal threshold for glucose falls 32 mg. per cent below the normal threshold.

*Presented at the joint meeting of the Chicago Gynecological Society, the Chicago Pediatric Society, and the Chicago Diabetic Association, Nov. 19, 1954.

A diminished tolerance for sugar may be considered an additional factor in the production of glycosuria in the pregnant woman. This opinion has resulted from many studies of the glucose tolerance curve during pregnancy and the ability of the gravid woman to tolerate glucose or galactose. In some instances a "lag" or "delayed glucose tolerance curve" is obtained. Because slow absorption and reduced gastric motility are frequently encountered during pregnancy, the intravenous type of test is preferred by some investigators.

In an attempt to study the effect of normal pregnancy on carbohydrate metabolism, Hurwitz and Jensen[5] did glucose tolerance tests in each trimester of pregnancy, two weeks after delivery, and several months post partum in a series of healthy pregnant patients. The fasting blood sugar levels during pregnancy were well within normal limits. Most of them were in the low-normal range, over half were under 90 mg. The peaks, too, were within normal limits. During pregnancy, a high percentage of abnormally elevated values for sugar at the two-hour level was found. This was particularly true during and after the second trimester. Two-hour levels as high as 164 were recorded. There was no significant elevation of the two-hour level during the postpartum period. The three-hour level was normal during pregnancy and following delivery.

Another condition which must be distinguished from renal glycosuria and diabetes is lactosuria. This is not common in pregnancy except during the last six weeks. At this time the incidence may be 7 per cent. Lactosuria is most frequent and marked in the puerperium. Rowe[2] was able to show its presence in 100 per cent of specimens on the third and fourth days post partum. It has been determined that the amount of lactose excreted is usually less than 100 mg. per cent before delivery, and more than 100 mg. during the early puerperium. Recently Flynn, Harper, and De Mayo[6] studied the excretion of sugars in the urine during pregnancy and the puerperium by paper partition chromatography. Specimens of urine were obtained from 245 pregnant women, 240 nonpregnant women, and 132 males to act as controls. Nine per cent of the controls both male and female had detectable quantities of lactose in the urine, while 50 per cent of the pregnant females showed lactosuria.

The incidence of lactosuria increased steadily from the third month until the thirty-fifth week, when 64 per cent of the patients showed lactosuria. The mechanism responsible for the excretion of lactose in the urine is not clearly defined. It is believed that lactosuria results either from synthesis of lactose in the mammary glands or from absorption of lactose from the intestine without prior splitting into glucose and galactose.

Of considerable importance is the possible relationship of renal glycosuria to the future development of diabetes mellitus. It has been recognized for some time that pregnancies in women who subsequently develop diabetes are associated with high fetal mortality rates and large infants. The nature of the factor responsible for the increased birth weight and the increased fetal mortality in prediabetic pregnancies remains unknown. There is some evi-

dence to support the observation that the functional strain on insulin production during repeated pregnancies may result in permanent diabetes. This is most likely to occur in the obese woman with a familial history of diabetes. It is generally agreed that maternal weight gain is not responsible for excessive fetal size. The incidence of large babies in obese mothers, however, is much greater than in nonobese women.

Experimentally,[7] it has been shown that repeated injections of extracts of the anterior pituitary into puppies produce, first, excessive growth, and, if continued—diabetes. It is possible that in the pregnant diabetic patient increased activity of the anterior pituitary may be responsible for the large size of the fetus, and also for the hypertrophy of the islets of Langerhans, a common postmortem finding in these infants. The same pituitary overactivity could be responsible for the large infants of prediabetic women, and the subsequent development of maternal diabetes.

In Miller, Hurwitz, and Kuder's[8] series of 137 pregnant women there were 11 patients who showed glycosuria but had normal glucose tolerance curves. Among this group 4 fetal deaths were recorded, and 3 of the infants weighed over 5 kilograms at birth. Such findings are contradictory to the idea that renal glycosuria during pregnancy is a "benign" condition.

References

1. Williams, E. C. P., and Wills, L.: Quart. J. Med. **22**: 493, 1929.
2. Rowe, A. W., Gallivan, D. E., and Matthews, H.: Am. J. Physiol. **96**: 94, 1931.
3. Batilwalla, K. C.: Indian M. Gaz. **82**: 191, 1947.
4. Eastman, N. J.: Obst. & Gynec. Surv. **1**: 3, 1946.
5. Hurwitz, D., and Jensen, D.: New England J. Med. **234**: 327, 1946.
6. Flynn, F. V., Harper, C., and De Mayo, P.: Lancet **2**: 698, 1953.
7. Young, F. G.: Biochem. J. **39**: 515, 1945.
8. Miller, H. C., Hurwitz, D., and Kuder, K.: J. A. M. A. **124**: 271, 1944.

Discussion

DR. ARTHUR R. COLWELL.—As I tried to prepare something interesting or at least appropriate for a discussion of this subject, I wondered whether the title, "Significance of Renal Glycosuria in Pregnancy," referred to physiological significance or clinical significance. I presume the answer probably is to both.

From the physiological standpoint there is not a great deal to say because there is not much known. Experience with renal glycosuria in pregnancy, just as in the nonpregnant woman, indicates that it is the same anomaly, at least from the chemical standpoint. The essential defect seems to be in an impaired tubular reabsorptive capacity.

In 1943, Mirsky reported some pertinent observations. A thorough study of 3 cases of renal glycosuria in nonpregnant women indicated that tubular reabsorption of sugar was about 75 to 95 mg. as compared with 240 to 340 mg. in the normal. Glucose was sliding past the tubules, probably because of a defect in the phosphorylating mechanism of the tubular cells.

Clinically we stand upon safer ground because we know more about the behavior of this condition and its significance to the mother and others concerned. There are essentially two points, as I see the problem. First of all, as Dr. Paul has pointed out, one must be on the alert not to treat diabetes as renal glycosuria. A good many obstetricians have been embarrassed because of having missed true diabetes mellitus by assuming that a renal glycosuria of pregnancy existed. One can be sure only by watching the blood sugar levels. The other clinical danger, of course, is in the treatment of the diabetic mother during pregnancy. A low threshold for sugar may permit glycosuria even when the blood sugar levels are normal. The only safe criterion for insulin effect is the blood sugar level.

White's interesting paper was most provocative and stimulating. I have always felt that it was hazardous for others to offer opinions because of her vast experience in this field. She has had many more patients and has done more meticulous experiments than others working in this field. To me the interesting thing has been not the treatment of the diabetic mother, or the salvage of her baby, although these things certainly are important. One must be aware of the fundamental significance of what she has reported in the field of endocrine physiology. If hormone-treated diabetics profit to the extent that she visualizes, the significance of that fact reaches far beyond the pregnant diabetic woman.

My own experience with mothers who have diabetes is largely restricted to the last three groups in her classification. In a group of some 30 or 40 severely diabetic pregnant patients during a period of ten years or so, I have been disappointed in the results of hormone therapy. The results have been uniformly bad as regards fetal survival. In both hormone- and non-hormone-treated patients we were not able to save more than 50 or 60 per cent of the babies. I am perfectly willing to admit that our results may have been due to the fact that we were not able to give the meticulous care that Dr. White has outlined. Certainly they have not had comparably large doses of hormone.

On the other hand, because of the potential physiological importance of what she has presented in the last ten or fifteen years, I am disappointed to hear her say that our friends across the sea have made her decide not to run a control or untreated series which would serve the purpose of counterproof. I would like to see her run a substantial series of cases now, treated in every respect the same as she would if sex hormones were used, but omitting the hormones. It seems to me that she has an obligation to satisfy herself and her critics as to the fetal salvage rate under such conditions. Others have reported it to be as good as her results with hormones.

THE NEWBORN OF DIABETIC MOTHERS*

ALVAH L. NEWCOMB, M.D., WINNETKA, ILL.

THERE have been advances in the medical management of maternal diabetes, obstetric care, and pediatric care, but a relatively high stillbirth and neonatal death rate has persisted. The fetal wastage still varies from 11 per cent to 30 per cent.

The pathologic abnormality of the infant of the diabetic woman is most striking in the lungs and pancreas. The pathologic picture in the infant pancreas may be nonspecific, but it is often remarkable. The islets are occasionally huge—generally much larger than the islets of infants with erythroblastosis fetalis. Recently McKay[1] has described an eosinophilic cellular infiltrate, Charcot-Leyden crystals, and dispersion of the beta cells throughout the islet, in contrast to the usual location of the beta cells in the center of the islet. The inflammatory eosinophilic infiltrate may give rise to Charcot-Leyden crystals.

The pathologic picture in the lungs varies from complete atelectasis of both lungs in the small premature infant to a lesser degree of pulmonary hyaline membrane disease in the older, larger infant who survives two or three days. There is usually extensive atelectasis in a large percentage of the alveoli; most of the remaining alveoli are lined with hyaline-staining material 10 to 20 microns thick.

Lowrey[2] of the University of Michigan reported that infants of diabetic mothers had "extremely variable plasma chloride and total base levels and a high proportion of these had an uncompensated acidosis with a lowered pH when compared to the normal newborn infant. The high CO_2 tension indicates that ventilatory control of this factor was lacking whether the fault be central or pulmonary." Furthermore, they stated that "there appears to be a direct correlation between the degree of infantile acidosis and the severity of the abnormal clinical picture present." They state that the exact cause of this acidosis is not at present clear.

The clinical picture of these babies varies tremendously. Generally the infants of mothers with the greatest edema, hypertension, and polyhydramnios develop the syndrome with which we are concerned. The newborn infant who develops pulmonary hyaline disease may need some help in respiration, but the infant who cries spontaneously often does too. The infant may be restless and whining or he may be lethargic. Retraction becomes more marked, the

*Presented at the joint meeting of the Chicago Gynecological Society, the Chicago Pediatric Society, and the Chicago Diabetic Association, Nov. 19, 1954.

cyanosis deepens, and death ensues shortly thereafter. However, there are some babies who, having had these symptoms, slowly improve in two or three days and make a complete recovery.

When convulsions develop in an infant previously doing well, particularly if maternal diabetes has been undiagnosed or poorly managed, hypoglycemia may be the cause. A badly spastic infant or death may be the result occasionally.

Experience accumulated in many clinics over the years suggests the following management:

Consultation between the internist, the obstetrician, and the pediatrician to determine the optimal day for delivery, which is usually between the thirty-sixth and thirty-eighth week.

Minimum analgesia and anesthesia. Since the infant is usually premature and often acidotic, respiratory depression may be anticipated.

Postural drainage, clearing the airway, and stripping the cord, which are customary procedures, are mandatory in these infants. Gastric aspiration on the resuscitation table is also mandatory, and it should be repeated for the first few hours if necessary.

The infant should be transferred immediately to a humid incubator.

Antibiotics may be prescribed, especially if there has been resuscitation and there are signs of respiratory distress.

Feedings are delayed twelve to forty-eight hours depending on the condition of the infant. Glucose, 2½ to 5 per cent, is given by dropper, nipple, or gavage at twelve hours in the stronger infant but is delayed in the infant who is retracting. Half breast milk and then breast milk follow as soon as the infant tolerates glucose.

The relatively high fetal death rate of infants of diabetic mothers is attributed to many factors. The exact etiology is not yet fully established. Until such time as more is known of the metabolism of these newborn infants, the foregoing therapeutic measures are our best hope.

References

1. McKay, Donald G., Benirschke, Kurt, and Curtis, George W.: Obst. & Gynec. 2: 133, 1953.
2. Lowrey, George H., Graham, Bruce B., and Tsao, M. U.: Pediatrics 13: 527, 1954.

Discussion

DR. MATTHEW M. STEINER.—The high fetal mortality still remains a perplexing problem in the management of diabetes during pregnancy. Many factors have been proposed, some based on purely anatomical alterations in the infant—while others are derived from biochemical investigations on rather small groups of infants. There is as yet no general agreement as to the basic disturbances in the newborn infant of a diabetic mother, and particularly the role of diabetes per se in the frequency of stillbirth or of cyanosis from respiratory distress, and at times fatal shock in the infant.

The juvenile patient with severe diabetes with vascular changes is particularly prone to toxemia and to high fetal wastage. Toxemia is then one of the contributing factors in fetal mortality but it is not the sole factor. The high incidence of intrauterine deaths between the thirty-fourth and thirty-seventh weeks has prompted many to interrupt the pregnancy with whatever method is deemed advisable—but this has created new problems for the premature infant.

Many anatomical aberrations have been proposed, none of which collectively explain adequately the "lethal" factor which must be responsible for the increased fetal mortality. Syndromes of macrosomia, cardiomegaly, visceromegaly, hematopoiesis of the liver, and hyperplasia of the islets have been described. While excessively large bodies do occur commonly in the diabetic patient, it is unusual that dystocia alone is the cause of death. Again, not all diabetic mothers give birth to large babies—nor is there a direct correlation between the size of the infant and the cardiomegaly or visceromegaly. There is no doubt that these heavy infants have more adipose tissue in addition to some edema, and the etiology may well be the increased growth hormone, which in the mother may be responsible for the diabetes while in the infant it gives rise to macrosomia.

The incidence of cardiomegaly has been stressed by Miller and Wilson, but there are decided objections to attributing the fetal mortality to changes in the heart, viscera, islets, or liver. For one, there is the prime difficulty in judging the size of the heart by the roentgen shadow in the young infant. Again, evidence of cardiac failure and/or embarrassment was notably lacking. Islet hyperplasia may be noted in conditions other than diabetes—and it is possible that the whole syndrome may not be related to any single factor. It is perplexing to note that the infants reported by Miller and Wilson did well when placed in oxygen because of respiratory distress and cyanosis, had large hearts on x-ray, and at autopsy no definite pulmonary lesions were reported.

Pulmonary hyaline membrane has been proposed by Winter and Gellis as the characteristic pathology in the infant with respiratory distress, and there is general agreement that this is the pathological picture in large series of infants examined. Yet some of the infants who clinically have something resembling "hyaline membrane disease" go on to recover slowly. It is interesting that the European literature has little reference to this entity. One may ask what environmental or intrinsic factor are responsible for the production of the intra-alveolar hyaline membrane, and also what biochemical changes are evidenced when an infant recovers from hyaline membrane disease. In the figures reported by Winter and Gellis as to the frequency of hyaline membrane in infants delivered by cesarean section of diabetic and nondiabetic mothers it is not clear what role diabetes itself plays in setting the intra-alveolar stage for the formation of a membrane. If we compare the figures of Blystad and others as to the frequency in casarean section in normal women we find that there is not much difference. Some clue as to the mechanism of production of hyaline membrane may be found in a recent report by Stevenson and Laufe on the experimental production of hyaline membrane which suggests that aspiration of amniotic fluid plus intra-alveolar exudation (from intense capillary engorgement) may be necessary. This brings up a vascular element which will be referred to later.

In recent years, biochemical investigations have demonstrated many interesting facts about the newborn of the diabetic mother, but the "lethal" factor still remains a mystery. It was customary at one time to attribute fetal mortality to hypoglycemic shock, and the initial therapy with concentrated glucose was directed to overcoming the threatening fall in blood glucose. Recent studies of the normal variation of blood glucose in normal infants have minimized the role of hypoglycemia. Similarly, Miller and Wilson, Gellis and Smith found no correlation between the clinical picture, clinical syndrome or electrolyte pattern, and the level of the blood sugar. More recently, Komrower of Manchester found wide variations in the blood sugar of these infants as compared with that in normal infants. A very interesting study of the blood sugar during the first day of life in infants of diabetic mothers has been done by Pedersen of Copenhagen. The configuration of blood

sugar curves was the same in diabetic and normal cases when the infants were kept under standard conditions. The average blood sugar during the first day is inversely proportional to the average blood sugar level of the mother during the last months of pregnancy and directly proportional to the average blood sugar level at delivery. The blood sugar levels are also proportional to the birth weights—inversely proportional in infants of diabetic mothers and directly proportional in those of normal mothers. Because of the varying blood sugar levels and the correlations found in this study, no generalizations can be made concerning the question whether the blood sugar is lower in the infant of the diabetic mother. There was also no correlation between the pathological symptoms and the blood sugar level during neonatal periods.

Biochemical data and electrolyte surveys have failed to demonstrate that in the infant of the diabetic mother there occurs a state of hyperpituitarism with secondary hyperadrenocorticism and consequent hypernatremia and hypokalemia. It would be very gratifying to attribute the entire clinical picture in the severely distressed infant to such alterations in electrolytes and water. Observations of Cook and Smith and others have shown that Na, K, and Cl excretion was greater in infants of diabetic mothers when compared with that of normal infants of comparable weight, but was the same as in normal infants of comparable gestational age. Urine volumes and weight losses were greater in infants of diabetic mothers. Here, too, if the sodium and chloride excretions following birth are used as indices of edema per kilogram of body weight, it is seen that infants of diabetic mothers have approximately the same amount of edema per kilogram that one would expect for their gestational age, although definitely more than the normal infant of the same weight. Again, individual variations within the group of diabetic infants were considerable, and there was no constant relationship between the excessive birth weight and the water or electrolyte excretions during the first three postnatal days. Moreover, these conclusions are conditioned by the fact that this work was done on infants not too severely distressed after birth.

Bjorklund, in a study of 10 of 15 cases, found "abnormal" electrocardiograms suggestive of hyperkalemia. In 4 of these cases the serum K was low. However, it is fairly well agreed that the ECG is an unreliable indicator of serum K changes and the interpretation of ECG even in the normal infant often leads to errors.

In a study of the chemical homeostasis of infants of diabetic mothers, Lowrey and others concluded that there is a lowered pH and uncompensated acidosis in many distressed infants while there is great variability in the range of plasma chloride and total base. These findings do not indicate that there is retention of total base and hence do not support a hypothesis that there is overactivity of the adrenal cortex with sodium retention, lowered K, and consequent ed ma. The lowered pH and relatively normal bicarbonate would also tend to rule against the accumulation of large amounts of acid metabolites as a cause of the uncompensated acidosis; i.e., there exists rather a high partial pressure of CO_2. This might be the result of pulmonary edema and/or atelectasis causing retention of CO_2 or the result of cerebral edema. Such a metabolic disturbance would tie in with hyaline membrane disease but the exact mechanism is also not definitely established.

Ditzel, White, and Duckers recently reported on the changes in the pattern of the smaller blood vessels in the bulbar conjunctiva in children of diabetic mothers. These changes were noted particularly in the capillaries and venules and ranged from elongation and irregularities to edema, hyaline infiltration, distention with slowing of the blood flow, and hemorrhage. There appeared to be a positive correlation between the severity of the vascular changes and abnormality of the glucose tolerance test. There was also a positive correlation between the degree of vascular change and the degree of growth and development. Whether these vascular changes represent primarily an inherited defective vascular tree or the effect of hormonal insult remains to be answered. It is interesting to speculate whether such changes as are noted in the bulbar conjunctiva may be in some infants associated with similar and severe changes in the capillaries of the brain or alveolae, and as such may account for alveolar and cerebral symptoms.

General Discussion on Papers of Drs. Priscilla White, Jerome T. Paul, and Alvah Newcomb

DR. JORGEN PEDERSEN, Copenhagen, Denmark.—In 1946, we began our clinical research on the diabetic pregnant woman in Copenhagen. We wanted to see how the classical treatment of these diabetic patients during pregnancy could influence the result of pregnancy, and we decided to keep the mothers in the hospital for the last eight weeks of pregnancy and to treat them as meticulously as we could. The patients come in in all stages of pregnancy, so we divided our group into two classes, those treated for a long time, and those treated for a short time, and the differential period of time was the fifty-third day from estimated date of delivery. All patients who came in for the first time before the fifty-third day were placed in the long-term group, and those who appeared after that time were put into the short-term group. On the average the long-term group was treated for 45 days and the short-term group for only 15 days.

With the so-called classical treatment we keep the blood sugar down to an average level of about 133 mg. per cent. We make four blood sugar determinations every day, and then on the third postpartum day one pregnanediol determination. There is no relationship between those who had endocrine therapy as opposed to those who did not. The only difference is the length of treatment. The patients in the short-term group had a higher blood sugar level than those in the long-term group.

We have used White's classification, especially for the severe cases, classes C, D, and F, according to the vascular picture. There is no major difference between the two groups.

In 75 per cent of the cases the membranes were ruptured; 17 per cent went into labor spontaneously; 10 per cent had cesarean sections, and we had the usual obstetrical indications for these. In the earlier cases we used to put these infants into an incubator for twenty-four hours to keep the oxygen and humidity up, but for the last eight years we have not used that procedure. We do not touch them.

We have 354 babies that weighed 1,000 grams or more. The fetal mortality on the tenth neonatal day was 28 per cent. The over-all mortality fell from 38 to 27 per cent in the cases of the long-term treatment. In the last few years it fell to 18 per cent. But now in the long-term patients it is much greater than it was. We are of the opinion that this is due to the treatment, but I do not know. Meticulous treatment helps, because we have 100 patients with a mortality of about 11 per cent. That means that the survival is 89 per cent. We have 117 patients with a fetal mortality of about 36 per cent. It seems that treatment helps.

We found that hydramnios was substantially reduced in the long-term group, but it did not disappear. We found that the severe cases of toxemia were fewer in the long-term group. Then we found that there were more losses in the babies in the long-term group than in the short-term group about 20 days before estimated delivery date. The long-term babies weighed on the average between 140 and 200 grams less.

In the long-term group we have only 5 per cent mortality, and the reason that this mortality is so low is that our babies weighed about 3,500 grams. The average time of delivery for all our patients was about three weeks before estimated delivery date.

We have found that the blood sugar levels were no more unstable than in other patients. I told you that we made four blood sugar determinations from each mother during the last 45 days. That means that the blood sugar for the infant is determined by conditions and appears as a negative correlation between these two, meaning that the higher

the blood sugar of the mother, the lower the blood sugar of the infant. We found by continuing to take blood sugar determinations in infants even when they are cyanotic there is absolutely no correlation between the blood sugar and clinical symptoms.

DR. PRISCILLA WHITE.—Two facts I would like to bring out. One of these Dr. Reis does not know, the other I am afraid he did not hear tonight. These facts concern a table of fetal survival published before 1936 and its statistics to which he referred.

Nearly all of the internists who have studied the problems of the obstetrical diabetic patients have thought that good chemical control of diabetes results in high fetal survival. I, too, published such a table—the one to which Dr. Reis refers. What he does not know, because it was not published, is this. Two years following that statement, with good chemical control our fetal mortality rose. At that time we sought elsewhere for causes of fetal fatalities.

Tonight I tried to present the difference in the character of the obstetrical population seen prior to 1936 and of the population which is seen at the present time.

Dr. Colwell very wisely pointed out the need for carefully controlled re-experiments. We hope we are taking part in such a program at the present time, through the American Medical Association. About forty clinics interested in obstetrical diabetics are taking part in it. There are three groups, agnostics who believe there is nothing helpful in female hormone therapy, who will continue not to give it; those who are believers, who will continue to manage their patients with these hormones; and the neutrals who will treat their cases alternately with and without hormones. Ultimately all of these reports will be submitted for statistical analysis, and we hope something good will come out of it. Thank you.

LONGITUDINAL STUDIES OF PREGNANCY ON THE ISLAND OF KAUAI, TERRITORY OF HAWAII*

I. Analysis of Previous Reproductive History

J. YERUSHALMY, PH.D., JESSIE M. BIERMAN, M.D., DOROTHY H. KEMP, M.D., ANGIE CONNOR, M.D., AND FERN E. FRENCH, M.A., BERKELEY, CALIF.

(From the Divisions of Biostatistics and Maternal and Child Health, School of Public Health, University of California, Berkeley, California, and the Division of Hospitals and Medical Care and the Bureau of Maternal and Child Health, Department of Health, Territory of Hawaii)

THE relatively slow pace with which progress is being achieved in the reduction of fetal and neonatal mortality is attributable to a lack of definitive knowledge of underlying causal factors, especially in the group of antepartum deaths. Few, indeed, are the conditions which have been demonstrated definitely and without ambiguity to be responsible for these latter fatalities. Even when postmortem examinations are performed with meticulous care by the most expert, the results usually throw light on the immediate causes of death only, leaving still unexplained the underlying factors and the train of events leading to it.[1-6]

One reason for this deficiency is the lack of opportunity to make clinical observations on the fetus to supplement pathological findings. When death occurs after extrauterine life has been well established, opportunity is provided for clinical observations in addition to postmortem examinations. When death occurs in utero or shortly after birth, however, clinical observations are limited to those that can be made of the mother.

The problem is further complicated in that at least two individuals must be observed, the fetus and the mother. The syndrome of causes and conditions which relate to fetal and neonatal mortality is traceable, in part, to the state of health of the mother and to genetic factors in both parents.[7-9] During the most crucial developmental period the fetus is confined to, and is affected by, the internal environment of the mother. If the external environment has any effect on the fetus, it must be transmitted through her. The deficiencies which may exist in the intrauterine environment, added to the weaknesses of the fetus which may be due to defective germ cells, and the special hazards due to the change from intra- to extrauterine life, present an extraordinarily complicated set of circumstances.

Because of the interdependence of fetus and mother, it is very difficult to establish directly *cause-and-effect* relationships. Instead, it is necessary to investigate, indirectly, *associations* between factors in the mother and outcome

*These studies are being financed through a grant from the Children's Bureau, Department of Health, Education and Welfare, and are operated cooperatively by the School of Public Health, University of California and the Department of Health, Territory of Hawaii.

of pregnancy. Even these often suffer from the fact that it is not possible to investigate these relationships in their proper chronological order from mother to fetus; rather, they are often inferred by investigating the circumstances "after the event" through retrospective studies.

These considerations led to the formulation and design of the Kauai study which will form the basis for a series of reports of which this is the first. The basic conviction was that a plan for a study of the continuum of pregnancy needed to be evolved which would start, not with the termination of pregnancy, but with its inception. The basic methodology would be that of a longitudinal investigation. The mother and the infant would be considered as a single entity because neither can be studied adequately without the other. Observations would begin as close to conception as possible, carry through the termination of pregnancy, and continue to at least the end of the first year of the infant's life. Special attention would be given to the early months of pregnancy since little is known about this period. Such a study should be undertaken on a community-wide basis because it is essential to consider fetal deaths and other accidents of pregnancy not as isolated instances but in the setting of all the pregnancies of which they form a part.

The difficulties of such an undertaking were realized from the beginning, but it was thought justifiable to expend considerable effort to investigate the feasibility of such a study. It was hoped that, as a minimum, it would furnish reliable data on the frequency of early fetal deaths in the different weeks of pregnancy, and would provide valuable experience in the conduct of studies in this difficult area. In addition, it would afford an opportunity to evaluate the usefulness and limitations of retrospective studies of pregnancy. Such studies which are based on data derived by recalling past events, if found reliable, would provide an efficient and economical method for obtaining much valuable information. Accordingly, an investigation was initiated on one of the Hawaiian Islands which combined both the longitudinal and retrospective approaches.

It is the purpose of this paper to present an evaluation and analysis of the information obtained through the retrospective study concerning the previous pregnancies of the women on this island. The data were subjected to a number of tests and were found to be reliable and complete for the purposes of this study. Accordingly, they were utilized to investigate the effect of order of pregnancy and age of mother on early fetal deaths and on childhood mortality, thus extending in both directions the known effects of these characteristics on late fetal* and neonatal mortality rates. Further, other characteristics, such as interval between pregnancies and outcome of previous pregnancies, were studied to determine their effects on early fetal, late fetal, infant, and childhood mortality.

*Fetal deaths are studied in this paper in two groups, those of less than 20 weeks' gestation and those of 20 or more weeks' gestation. These are referred to in the text as "early" and "late" fetal deaths, respectively. It should be noted, however, that the term "late fetal death" as used here differs from that recommended by the World Health Organization. The latter defines late fetal deaths as those of more than 28 weeks of gestation. The term "late" is used here only as a convenience, to avoid repeating "intermediate and late fetal deaths."

Material

This study is being conducted on the Island of Kauai, Territory of Hawaii. The relatively stable population of the island, which numbers around 30,000, consists of several racial groups. The island is rural in character, the main industries being large pineapple and sugar cane plantations. The death rates are relatively low, including those for fetal and infant mortality. The island is served by a local health department, with a staff which includes seven public health nurses.

The reason for the selection of this island lay in the belief that the identification of pregnant women early in pregnancy could more easily be accomplished here than elsewhere because of the close relationship between the health department personnel and the community. Also, the attitude toward pregnancy in the island was thought to be more natural and less inhibited and therefore more complete and early reporting of pregnancy might be expected. In addition, the population has the benefit of good medical care coverage, and the cooperation of the medical profession of the island was anticipated. These considerations were thought to outweigh such disadvantages as might result from the fact that the population is not representative, especially with respect to racial composition.

The first step in the study consisted of a complete census of the population. For each individual and for each household unit, certain minimum information was obtained. Further, for each woman 12 years of age and over, a reproductive history was obtained on a special form specifying the outcome of all pregnancies by dates and including all early and late fetal deaths. Information was also obtained on all women who were pregnant at the time of the census. During the process of enumeration, the interviewers explained the purpose of the study to the women and sought their cooperation for the next step, namely, the reporting of their future pregnancies as soon as they become aware of the fact.

The present investigation is based on data relating to the previous reproductive history which was obtained for all women who had experienced at least one pregnancy. This information was obtained by enumerators who were not professional interviewers. They were intelligent women, residents of the island, whose experience in interviewing was limited to such as would normally be encountered in their previous professions of nursing and social work. The preparation for their interviewing task consisted of making them aware of the purposes and importance of the study, outlining the more common pitfalls, and emphasizing the necessity of helping each woman recall her complete reproductive history. They reviewed with each woman the sequence of reported pregnancies and inquired about any omissions, especially if long periods elapsed without a recorded pregnancy. It was felt that whatever was lacking in professional interviewing skills was compensated for by conscientiousness and acceptance by the community.

Tests of Reliability and Adequacy of the Data

The information provided by the women relative to their previous pregnancies may be tested in two ways. First, the fetal, infant, and childhood mortality rates as derived from the reported previous pregnancies may be compared with similar rates obtained for the locality from recorded vital statistics. The data may further be tested by reviewing the variation of the derived rates according to such characteristics as age of mother and order of pregnancy to see whether they conform to known facts.

The 6,039 women in this study reported a total of 27,528 previous live births and fetal deaths, an average of 4.6 per fertile woman. Of these, 27.9 per 1,000 terminated in a fetal death at 20 weeks' or more gestation and 52.5 per 1,000 liveborn died before reaching the first birthday. The recorded stillbirth rates in the Territory were lower than 27.9 for the period since 1935, were around that level for the decade 1925-1934, and were higher prior to 1925. Since the fetal deaths reported in the retrospective study have occurred over a period of many years, the calculated rate of 27.9 appears to be reasonable. Similarly, the rate of 52.5 for infant mortality agrees well with the trend of recorded rates for the Territory during the past 30 years. Mortality rates past the first year of life also accord well with those calculated from vital records. It may be stated, therefore, that the women have not understated their previous late fetal and infant losses to any considerable extent. Nor were discrepancies discovered in the data when studied separately for the different racial groups. A comparison of the rankings by race, for infant mortality and for late fetal deaths as derived from the present study and as reported through official vital statistics records, show remarkable agreement.

The situation is somewhat different with regard to early fetal deaths. Since no figures for comparison are available for the Territory, the calculated fetal death rates by weeks of gestation were compared with the reported fetal death rates in New York City—the only official data available in this country. The latter, however, may also be deficient since it is probable that early fetal deaths are not completely reported in New York City.[10] The data are therefore also compared with the information which is now becoming available on a small scale from the longitudinal study on Kauai. To date, data are available on 1,191 women who first came to the attention of the study while they were pregnant. Not all were observed for the entire duration of pregnancy, but a sufficient number have been under observation during each of the periods to make possible the calculation of fetal death rates by individual months of pregnancy. The comparison of the three sets of rates is shown in Table I.

TABLE I. RATES FOR EARLY FETAL DEATHS BY WEEKS OF GESTATION AS OBTAINED FROM THE KAUAI RETROSPECTIVE STUDY 1953, COMPARED WITH THE RATES REPORTED IN NEW YORK CITY IN 1949 AND WITH THE RATES OBTAINED FROM THE LONGITUDINAL STUDY ON THE ISLAND OF KAUAI, T. H., 1953-1954

WEEKS OF GESTATION	RATE OF 1,000 PREGNANCIES		KAUAI LONGITUDINAL STUDY 1953-1954	
	KAUAI RETROSPECTIVE STUDY 1953*	NEW YORK CITY FETAL DEATH CERTIFICATES 1949†	RATE‡	PERSON-MONTHS OF OBSERVATION
8-11	16.5	27.0	35.4	198.0
12-15	18.4	15.1	36.2	359.5
16-19	9.1	8.1	8.2	486.0
20-23	4.2	5.2	6.8	589.5
24-27	4.1	3.4	4.7	636.0

*In calculating these rates, 40 pregnancies for which the outcome was not recorded were excluded.

†Baumgartner, Leona, and Erhardt, Carl[23]; National Office of Vital Statistics: Vital Statistics of the U. S., 1949, Part I, p. 58.

‡Rate per 1,000 person-months of observation.

It is seen that the data from the retrospective study are deficient in early fetal deaths. Between the eighth and twelfth weeks of gestation, the rates for the retrospective study are somewhat smaller than those for New York City, and both are much lower than the rates obtained from the longitudinal study. Fetal deaths at 12 to 16 weeks of pregnancy were somewhat higher for the retrospective study than for New York City, but only half as high as the rates

in the longitudinal study. From the sixteenth to the twenty-eighth weeks of pregnancy the rates of fetal loss for the three groups are almost identical.

Actually, the volume of underreporting may not be as large as is implied by a comparison with the longitudinal study, since the latter is based on observations of only a small group. But it is obvious that considerable understatement of early fetal loss took place in reporting the previous pregnancies in the retrospective study.

TABLE II. RATES BY YEAR OF BIRTH OF MOTHER FOR FETAL DEATHS UNDER AND OVER 20 WEEKS' GESTATION, FOR INFANT DEATHS UNDER AND OVER 1 MONTH OF AGE, FOR CHILDHOOD MORTALITY (1-4 YEARS OF AGE), AND FOR DEATHS AT 5 YEARS OF AGE AND OVER AS DETERMINED FROM THE PREVIOUS REPRODUCTIVE HISTORY OF *All Mothers* ON THE ISLAND OF KAUAI, TERRITORY OF HAWAII, 1953*

YEAR OF BIRTH OF MOTHER	NUMBER OF LIVE BIRTHS AND FETAL DEATHS	RATES FOR FETAL DEATHS			RATES FOR INFANT DEATHS			RATES FOR CHILDHOOD MORTALITY	DEATH RATES AT 5 YEARS OF AGE AND OVER
		UNDER 20 WEEKS	20 OR MORE WEEKS	TOTAL	UNDER 1 MONTH	1 MONTH TO 1 YEAR	TOTAL		
After 1929	859	72.2	21.3	92.0	19.2	5.2	24.4	3.9	—
1920-1929	5,441	56.6	24.5	79.8	10.2	6.9	17.0	4.5	1.0
1910-1919	5,852	57.4	24.1	80.1	17.7	14.8	32.2	12.1	8.0
1900-1909	6,073	49.1	30.2	79.0	28.2	41.4	68.4	24.8	25.9
1890-1899	5,225	37.8	29.9	69.1	24.4	55.8	78.8	37.5	48.6
1880-1889	2,787	26.9	37.6	63.9	26.7	53.6	78.9	46.2	75.7
Before 1880	1,251	29.6	23.9	53.6	21.2	53.8	73.9	62.4	124.3
Total†	27,528	47.9	27.9	75.3	20.9	32.2	52.5	23.4	29.1

*In this and in the following tables, pregnancies with unrecorded or incompletely reported items of information were handled as follows: 40 pregnancies for which the outcome was not recorded were excluded completely (only 2 were in women under 50 year of age); 24 fetal deaths for which duration of pregnancy was not recorded were used in calculating total fetal death rates but not early and late fetal deaths (12 were in women under 50); 40 liveborn who died for whom age at death was not recorded were used in the denominator of the fetal death rates only (9 were born to women under 50).

Rates were calculated per 1,000; denominators of rates were as follows: total pregnancies—for total fetal death rates, and fetal death rates under 20 weeks; pregnancies of 20 or more weeks' gestation—for fetal death rates at 20 or more weeks' gestation; total live births—for total infant death rates and rates under one month; liveborn infants surviving first month—for infant death rates at 1 month to 1 year; children surviving first year of life—for childhood mortality at 1-4 years; and children surviving to age 5 years—for death rates at 5 years of age and older.

†Total includes 40 for which year of birth of mother was not recorded.

It becomes important, therefore, to determine whether this underreporting has been uniform or selective. Table II was constructed to test whether the age of the woman at time of census was related to underreporting. A review of the figures for each of the different indices is instructive. The rates for infant mortality, early childhood mortality, and mortality at 5 years of age and over, as well as for late fetal deaths (20 weeks' or more gestation), show a consistent pattern with respect to both magnitude and trend. The women, at least those under 70 years of age at the time of census, were able to recall and report their late fetal deaths and the deaths of their liveborn children with relative accuracy. The derived rates in general increase progressively with each decade of age, as would be expected from the trend of these rates over the years. The actual level of the rates is also in general agreement with recorded vital statistics. For women who were born before 1880, the information may not be quite as reliable since their data show somewhat lower rates in infant and fetal mortality.

As to fetal deaths at less than 20 weeks' gestation, it is obvious that the relatively low rate in Table I for the entire group results from the gross understatement of the older women. For women in the younger age groups the derived rates are much higher, and remain on a relatively high level for women born after 1900.

It may therefore be concluded that for purposes of studying the mortality experience of the liveborn and for investigating late fetal mortality, the experience of the entire group presents rates of acceptable levels. If interest is centered on early fetal mortality, however, it appears that a more reliable level is secured from the records of women who at the time of inquiry were younger than 50 years of age. Since in the present study attention is focused on the very early fetal deaths, it was thought wise to limit the analysis to data obtained from women born after 1903, i.e., women who were less than 50 years of age at the time of the census. This reduces the number of pregnancies available for study, but increases the reliability of data on early fetal deaths.

Another test of the adequacy and reliability of the data relates to the factors of order of pregnancy and age of mother at delivery. The variation of the late fetal and neonatal mortality rates by these factors has been studied by a number of workers with essentially similar results.[11-15] For this reason the present findings on order of pregnancy and age of mother as obtained from women who were less than 50 years of age at census are compared in Figs. 1 and 2 with those from New York State (exclusive of New York City).*

The similarity in the results of the retrospective study and the figures in New York State is striking. The slight deviations are explainable on the basis of small numbers. (The differences are not statistically significant.) This is all the more remarkable in view of the fact that there is a difference in definition of "order of birth." In the retrospective study all pregnancies are counted, while the figures for New York State relate only to pregnancies of 20 or more weeks' gestation. Moreover, the present study is based on a rural population which is racially heterogeneous, while the population of New York State (exclusive of New York City) is a much more homogeneous group racially and includes urban as well as rural residents. The similarity in results shown in Figs. 1 and 2 not only fortifies the confidence in the reliability of the data which the women furnished by recalling their previous reproductive histories, but it re-emphasizes the importance of these biological factors of age and order of pregnancy. Their effect seems to be universal in nature, not limited to any special group.

In summary, it was found that the information from women of all ages was reliable for all indices other than for early fetal deaths. Data obtained only from women who were less than 50 years of age were adequate also for the study of early fetal deaths. Consequently, only the records for women under 50 are utilized for the following analysis.

Order of Pregnancy and Age of Mother

From Figs. 1 and 2 it is seen that the order of pregnancy and age of mother at delivery strongly influence both the late fetal and the neonatal mortality rates. The rates start high for first births, are at a minimum for second and third births and increase thereafter with the higher orders of birth. As to age of mother, the late fetal and neonatal mortality rates are at their lowest for mothers in their twenties, and are higher for births to the younger and older mothers.

Data from the present study are available to investigate the effect of these factors also on early fetal deaths and on mortality of the older infants and of young children. Moreover, it is possible to compare the effect of these

*These figures were constructed on a relative basis; that is, they show the rates by order of pregnancy as percentages of the rate for all pregnancies, and the rates by age of mother as percentages of the rates for all ages, in each group. This allows the direct comparison of the variation of the rates by these characteristics for the retrospective study and for New York State without the complicating factor of the difference in the level of the rates.

factors on the early and late fetal and infant loss and to bring out the similarities and differences in these effects. These comparisons may be helpful in understanding and evaluating the effect of possible etiological factors. In general terms it may be stated that as we progress along the age scale from conception to birth, through infancy, to childhood, the effect of environmental factors probably increases, while the effect of such biological factors as may be operating to contribute to death may be decreasing. The influence of factors associated with delivery and the birth process (obstetrical factors) may be expected to be reflected mostly in late fetal and neonatal mortality. Consequently the relative effects of the different characteristics on one of the indices compared to their effects on the others may provide useful guides in the search for causative factors.

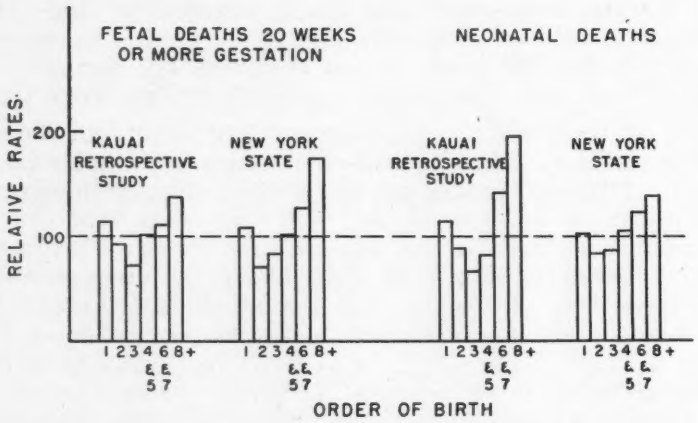


Fig. 1.—A comparison of findings from the Kauai Retrospective Study and from New York State. Relative rates by order of birth for fetal deaths at 20 or more weeks' gestation, and for neonatal deaths as obtained from the previous reproductive history of all mothers under 50 years of age on the Island of Kauai, Territory of Hawaii, 1953, compared with those of New York State (exclusive of New York City), 1936-1938.

Relative rates=rates as percentages of rate for total (all orders of birth) in each group.

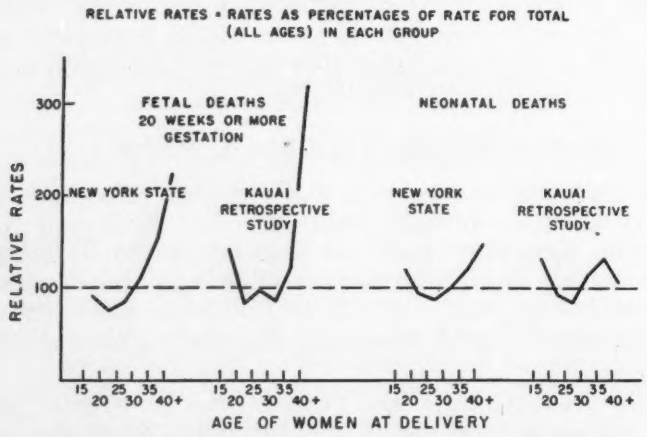

RELATIVE RATES • RATES AS PERCENTAGES OF RATE FOR TOTAL (ALL AGES) IN EACH GROUP
300
200
100
RELATIVE RATES
FETAL DEATHS 20 WEEKS OR MORE GESTATION
NEONATAL DEATHS
NEW YORK STATE
KAUAI RETROSPECTIVE STUDY
NEW YORK STATE
KAUAI RETROSPECTIVE STUDY
15 20 25 30 35 40+
AGE OF WOMEN AT DELIVERY

Fig. 2.—A comparison of findings from the Kauai Retrospective Study and from New York State. Relative rates by age of mother for fetal deaths at 20 or more weeks' gestation from the pregnancies of Order 2 or more in previous reproductive history of all mothers under 50 years of age on the Island of Kauai, Territory of Hawaii, 1953, compared with those of New York State (exclusive of New York City), 1936-1938.

Relative rates=rates as percentages of rate for total (all ages) in each group.

Order of Pregnancy.—The variation of early and late fetal death rates and of neonatal, postneonatal, and early childhood mortality rates, according to order of pregnancy are shown in Table III. Fig. 3 presents the same data in terms of relative rates in order to facilitate comparison of the different indices.

TABLE III. RATES BY ORDER OF PREGNANCY FOR FETAL DEATHS UNDER AND OVER 20 WEEKS' GESTATION, FOR INFANT DEATHS UNDER AND OVER 1 MONTH OF AGE, AND FOR CHILDHOOD MORTALITY (1-4 YEARS OF AGE) AS DETERMINED FROM THE PREVIOUS REPRODUCTIVE HISTORY OF *Mothers Under 50 Years of Age* ON THE ISLAND OF KAUAI, TERRITORY OF HAWAII, 1953*

ORDER OF PREGNANCY	NUMBER OF LIVE BIRTHS AND FETAL DEATHS	RATES FOR FETAL DEATHS		RATES FOR INFANT DEATHS		RATES FOR CHILDHOOD MORTALITY
		UNDER 20 WEEKS	20 OR MORE WEEKS	UNDER 1 MONTH	1-11 MONTHS	
1	4,234	50.1	29.6	19.7	16.7	8.0
2	3,593	57.9	23.9	15.4	12.3	8.4
3	2,729	60.1	19.1	11.5	16.5	10.6
4 and 5	3,055	58.3	26.1	14.3	13.8	12.5
6 and 7	1,112	58.5	28.7	24.6	27.2	13.5
8 or more	639	84.5	35.9	33.8	20.3	18.8
Total	15,362	57.3	25.9	17.1	15.9	10.3

*See first footnote under Table II.

A number of points of interest emerge. It is noted that the higher rates for first pregnancies are found mainly in late fetal and neonatal mortality, to a somewhat lesser degree in the postneonatal period and are absent completely in both early fetal and in childhood mortality. This suggests that the higher rates do not reflect weakness of the first-born infant but rather the specific obstetrical hazards of the first birth.

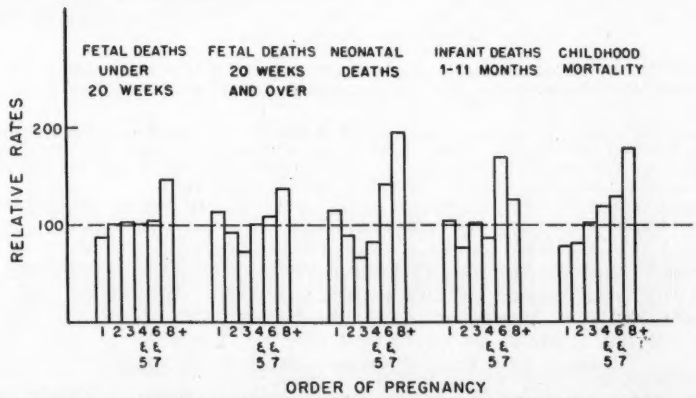


Fig. 3.—Relative rates by order of pregnancy for fetal deaths under and over 20 weeks' gestation, for infant deaths under and over 1 month of age, and for childhood mortality (1-4 years of age), as determined from the previous reproductive history of all mothers under 50 years of age on the Island of Kauai, Territory of Hawaii, 1953.

Relative rates=rates as percentages of rate for total (all pregnancies) in each group.

Early fetal deaths are influenced by order of pregnancy to a much lesser extent than any of the other indices. In fact, with the exception of first pregnancies and those of very high order, the early fetal death rates are only slightly affected by order of pregnancy. The pattern of childhood mortality at 1 to 4 years of age exhibits a very orderly and striking variation with order of pregnancies to an even stronger degree than that of the other indices. This indicates that the high rates for the high order of pregnancy may have an environmental origin.

Age of Mother.—A similar analysis by age of mother at the time of termination of pregnancy is shown in Table IV and Fig. 4. The striking thing here is that with regard to the age of the mother the early fetal death rates behave much like the late fetal rates. On the other hand, mortality rates of older infants and of children do not increase as the age of the mother increases. On the contrary, the rates decline continuously from very high values for the very young to low rates for the older mothers. This may indicate that the high rates of fetal and neonatal mortality among infants of older mothers are not entirely of an environmental origin. The fact that late fetal deaths are affected by the age of the mother much as early fetal deaths are affected by this factor points to possible biological influences of aging on reproductive wastage.

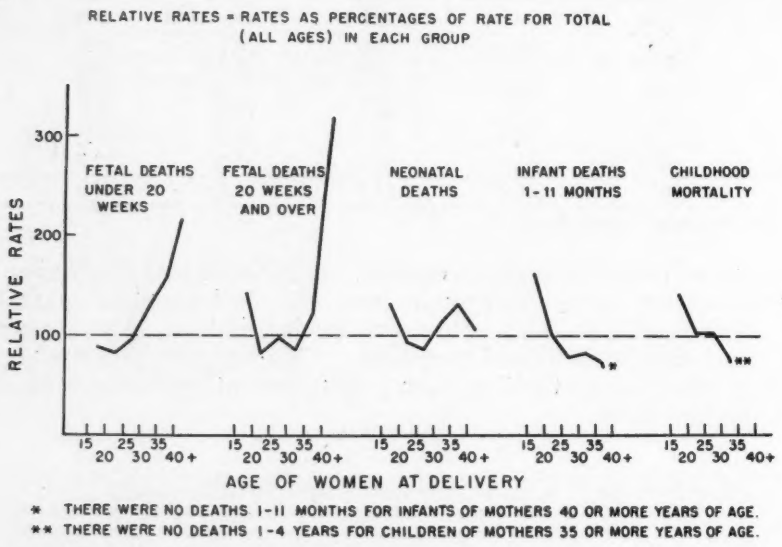

RELATIVE RATES = RATES AS PERCENTAGES OF RATE FOR TOTAL (ALL AGES) IN EACH GROUP
RELATIVE RATES
300
200
100
FETAL DEATHS UNDER 20 WEEKS
FETAL DEATHS 20 WEEKS AND OVER
NEONATAL DEATHS
INFANT DEATHS 1-11 MONTHS
CHILDHOOD MORTALITY
15 20 25 30 35 40+
AGE OF WOMEN AT DELIVERY
* THERE WERE NO DEATHS 1-11 MONTHS FOR INFANTS OF MOTHERS 40 OR MORE YEARS OF AGE.
** THERE WERE NO DEATHS 1-4 YEARS FOR CHILDREN OF MOTHERS 35 OR MORE YEARS OF AGE.

Fig. 4.—Relative rates by age of mother at delivery for fetal deaths under and over 20 weeks' gestation, for infant deaths under and over 1 month of age, for childhood mortality (1-4 years of age), as determined from the previous reproductive history of all mothers under 50 years of age on the Island of Kauai, Territory of Hawaii, 1953.
Relative rates=rates as percentages of rate for total (all ages) in each group.

TABLE IV. RATES BY AGE OF MOTHER AT DELIVERY FOR FETAL DEATHS UNDER AND OVER 20 WEEKS' GESTATION, FOR INFANT DEATHS UNDER AND OVER 1 MONTH OF AGE, FOR CHILDHOOD MORTALITY (1-4 YEARS OF AGE), AS DETERMINED FROM THE PREVIOUS REPRODUCTIVE HISTORY OF *Mothers Under 50 Years of Age* ON THE ISLAND OF KAUAI, TERRITORY OF HAWAII, 1953*

AGE OF MOTHER AT DELIVERY	NUMBER OF LIVE BIRTHS AND FETAL DEATHS	RATES FOR FETAL DEATHS		RATES FOR INFANT DEATHS		RATES FOR CHILDHOOD MORTALITY
		UNDER 20 WEEKS	20 OR MORE WEEKS	UNDER 1 MONTH	1-11 MONTHS	
Under 20	1,905	50.4	37.0	22.4	25.8	14.5
20-24	5,779	46.7	21.4	16.0	16.0	10.5
25-29	4,615	55.3	25.2	14.6	12.4	10.6
30-34	2,170	74.7	22.4	19.4	13.0	7.9
35-39	705	90.8	31.2	22.5	11.5	0.0
40 or more	137	124.1	83.3	18.3	0.0	0.0
Total†	15,362	57.3	25.9	17.1	15.9	10.3

*See first footnote under Table II.
†Total includes 51 with age of mother unknown.

Interval Between Pregnancies

The question of whether there exists an optimum interval between pregnancies in terms of the survival of the infant has not yet been settled conclusively. Studies conducted by the Children's Bureau[16] 30 years ago showed that the infant mortality rate was high when the interval between births was short and was at a minimum for intervals of around 3 years. Eastman,[17] in an analysis of data from the Johns Hopkins Hospital, was able to demonstrate a relatively high rate when the interval between births was under 12 months, but found no increase in the rate for other intervals. Yerushalmy,[18] in an indirect study, found evidence for the existence of an optimum interval; this study indicated that the stillbirth rates were high when the interval between births was either short or long, and low for moderate intervals. The method, however, was not suitable for determining quantitatively the optimum interval.

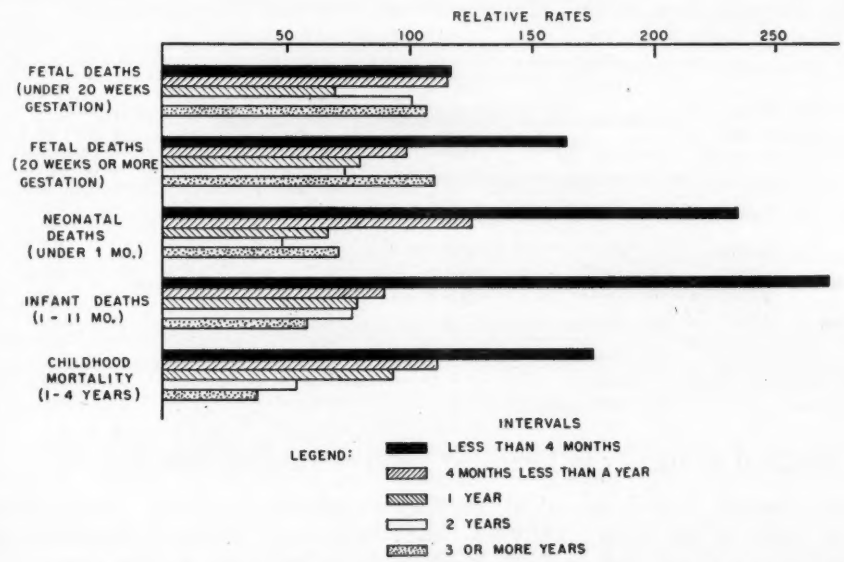


Fig. 5.—Relative rates by interval between the termination of one and the beginning of the next pregnancy for fetal deaths under and over 20 weeks' gestation, for infant deaths under and over 1 month of age, and for childhood mortality (1-4 years of age), as determined from the pregnancies of Order 2 or more in the previous reproductive history of all mothers under 50 years of age on the Island of Kauai, Territory of Hawaii, 1953.

Relative rates=rates as percentages of rate for total (all intervals) in each group.

The data on which this study is based provide information on interval between the termination of one pregnancy and the beginning of the next as reported on the special form. It was possible to construct rates for early and late fetal deaths, for neonatal, postneonatal, and for childhood mortality according to these intervals. These are shown in Table V and Fig. 5. A review of the rates is interesting. The value of each of the indices is high when the interval is very short (less than 4 months). Both late fetal and neonatal mortality rates are lowest when the interval from the termination of one pregnancy to the beginning of the next was between 2 and 3 years, which is equivalent to an optimum interval between births of around 3 to 3½ years. When the interval between pregnancies was 3 or more years, the rates were higher than for the more moderate intervals. In the case of late fetal mortality the rate for the longest interval was higher than for any of the other intervals except the very short one of less than 4 months. On the other hand,

in the case of early fetal deaths, the increase associated with the very short interval is not so pronounced and the lowest rate is found for an interval of between 1 and 2 years. The disadvantages of long intervals between pregnancies are not present for postneonatal and childhood mortality. The fact that for the short interval the postneonatal and childhood mortality rates are also high suggests that the reason for the high rates associated with the short interval may, in part, be of an environmental origin. The increase in the rates associated with long intervals which is found for fetal and neonatal mortality but not for postneonatal and childhood mortality, suggests that the reason for the high rates may be of a biological rather than of an environmental origin.

TABLE V. RATES BY INTERVAL BETWEEN THE TERMINATION OF ONE AND THE BEGINNING OF THE NEXT PREGNANCY FOR FETAL DEATHS UNDER AND OVER 20 WEEKS' GESTATION, FOR INFANT DEATHS UNDER AND OVER 1 MONTH OF AGE, AND FOR CHILDHOOD MORTALITY (1-4 YEARS OF AGE) AS DETERMINED FROM THE *Pregnancies of Order 2 or More* IN THE PREVIOUS REPRODUCTIVE HISTORY OF *Mothers Under 50 Years of Age* ON THE ISLAND OF KAUAI, TERRITORY OF HAWAII, 1953*

INTERVAL	NUMBER OF LIVE BIRTHS AND FETAL DEATHS	RATES FOR FETAL DEATHS		RATES FOR INFANT DEATHS		RATES FOR CHILDHOOD MORTALITY
		UNDER 20 WEEKS	20 OR MORE WEEKS	UNDER 1 MONTH	1-11 MONTHS	
Less than 4 months	1,124	70.3	40.2	37.9	42.5	19.5
4-11 months	3,599	69.7	24.2	20.2	14.1	12.4
1 year	3,673	42.2	19.6	10.7	12.3	10.4
2 years	1,286	62.2	19.1	7.6	11.9	6.0
3 or more years	1,347	64.6	27.0	11.4	9.1	4.2
Total†	11,127	60.1	24.4	16.1	15.6	11.1

*See first footnote under Table II.
†Total includes 98 intervals of unknown length.

Familial Tendency to Repeated Fetal and Infant Losses

Previous studies based on vital statistics records in New York State (exclusive of New York City) showed that there is a familial tendency to repeated fetal and infant losses.[19-20] Women who had had a fetal loss in a previous pregnancy or who had lost a child are more likely to have a fetal or neonatal death in a subsequent pregnancy than women whose previous issue have all survived. Studies of other populations have shown similar results.[21-22]

TABLE VI. RATES ACCORDING TO THE NUMBER OF PREVIOUS LOSSES FOR FETAL DEATHS UNDER AND OVER 20 WEEKS' GESTATION AND FOR INFANT DEATHS UNDER AND OVER 1 MONTH OF AGE AS DETERMINED FROM THE *Pregnancies of Order 2 or More* IN THE PREVIOUS REPRODUCTIVE HISTORY OF *Mothers Under 50 Years of Age* ON THE ISLAND OF KAUAI, TERRITORY OF HAWAII, 1953*

NUMBER OF PREVIOUS LOSSES†	NUMBER OF LIVE BIRTHS AND FETAL DEATHS‡	RATES FOR FETAL DEATHS		RATES FOR INFANT DEATHS	
		UNDER 20 WEEKS	20 OR MORE WEEKS	UNDER 1 MONTH	1-11 MONTHS
None	8,089	49.1	20.8	13.3	12.8
1	2,213	82.7	31.0	21.4	20.8
2 or more	812	108.4	44.2	31.8	32.8

*See first footnote under Table II.
†Fetal deaths and infant deaths in previous pregnancies.
‡Excludes 14 cases in which number of previous losses was not reported.

The present data are suitable for more extensive investigations of this phenomenon. First, it is possible to investigate whether early fetal deaths

are similarly affected by outcome of previous pregnancies. More important, it is possible to investigate the specificity of this repetitive character, i.e., whether the *form* of the previous loss tends to repeat itself.

In the first place, it may be interesting to note from Table VI and Fig. 6 that the results of this study are similar to those of other studies on the very strong repetitive character of reproductive wastage. Thus, when the births are divided into those in which the previous pregnancies resulted in infants who survived the first year of life and those which terminated in one or more fetal or infant deaths, the rates of loss in the subsequent pregnancy are greatly increased in the groups with previous fatalities. It will be seen that there is a sharp and almost identical increase with previous losses in each of the indices (early and late fetal, neonatal, and postneonatal mortality).

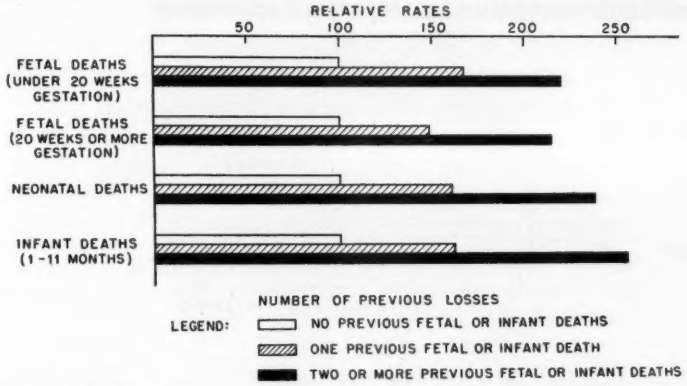


Fig. 6.—Relative rates according to the number of previous losses for fetal deaths under and over 20 weeks' gestation, and for infant deaths under and over 1 month of age as determined from pregnancies of order 2 or more in the previous reproductive history of all mothers under 50 years of age on the Island of Kauai, Territory of Hawaii, 1953.
Relative rates=rates as percentages of rate for no previous losses in each group.

The new findings of this study, however, are shown in Table VII and Fig. 7. These show the rates of loss in the current pregnancy according to the outcome of the immediately preceding pregnancy. It will be seen that *each of the forms of reproductive wastage is affected by a specific form of previous loss.*

TABLE VII. RATES BY OUTCOME OF THE IMMEDIATELY PRECEDING PREGNANCY FOR FETAL DEATHS UNDER AND OVER 20 WEEKS OF GESTATION, AND FOR INFANT MORTALITY, AS DETERMINED FROM THE *Pregnancies of Order 2 or More* IN THE PREVIOUS REPRODUCTIVE HISTORY OF *Mothers Under 50 Years of Age* ON THE ISLAND OF KAUAI, TERRITORY OF HAWAII, 1953*

OUTCOME OF IMMEDIATELY PRECEDING PREGNANCY	NUMBER OF LIVE BIRTHS AND FETAL DEATHS†	RATES FOR FETAL DEATHS		INFANT MORTALITY
		UNDER 20 WEEKS	20 OR MORE WEEKS	
Live birth: survived first year	9,723	51.0	21.7	28.5
Live birth: died under 1 year of age	396	53.0	24.0	95.6
Fetal death at 20 or more weeks' gestation	253	63.2	92.8	88.4
Fetal death under 20 weeks' gestation	651	193.5	34.3	17.8

*See first footnote under Table II.
†Excludes 75 cases in which the immediately preceding pregnancy terminated in a multiple birth and 30 cases in which the outcome of the immediately preceding pregnancy was not reported.

For example, rates for early fetal deaths are about the same when the outcome of the immediately preceding pregnancy resulted in an infant which sur-

vived the first year, or in an infant death, or in a late fetal death. The increase, and it is very large, occurs *only when the immediately preceding pregnancy also resulted in an early fetal death (less than 20 weeks' gestation).* Similarly, rates for late fetal deaths are about the same when the outcome of the preceding pregnancy resulted in an infant which survived the first year, or in an infant death, or in an early fetal death. The increase is found *only when the previous pregnancy also terminated in a fetal death at 20 or more weeks' gestation.* And finally, rates for infant mortality are about the same when the out-

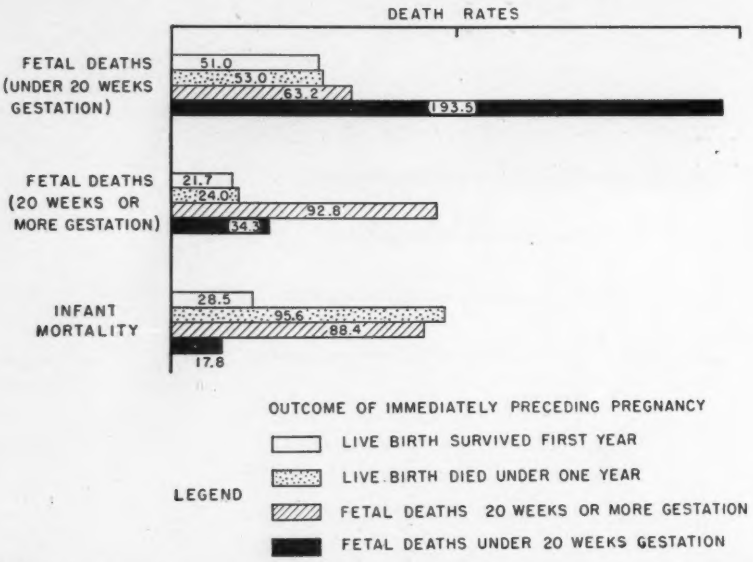


Fig. 7.—Rates according to outcome of the immediately preceding pregnancy for fetal deaths under and over 20 weeks' gestation, and for infant mortality, as determined from pregnancies of order 2 or more in the previous reproductive history of all mothers under 50 years of age on the Island of Kauai, Territory of Hawaii, 1953. Excludes cases in which the immediately preceding pregnancy terminated in a multiple birth.

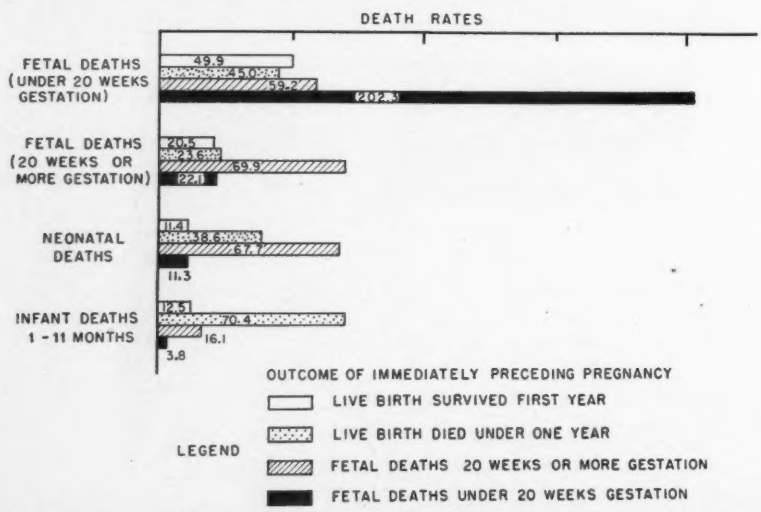


Fig. 8.—Rates according to outcome of the immediately preceding pregnancy for fetal deaths under and over 20 weeks' gestation, for infant deaths under and over 1 month of age as determined from the second and third pregnancies only, in the previous reproductive history of all mothers under 50 years of age on the Island of Kauai, Territory of Hawaii, 1953. Excludes cases in which the immediately preceding pregnancy terminated in a multiple birth.

come of the previous pregnancy resulted in a liveborn infant who survived the first year or in an early fetal death. The largest increase was found when the previous pregnancy also terminated in an infant death. A somewhat smaller increase is noted also when the previous pregnancy terminated in a late fetal death.

Table VIII and Fig. 8 present data of a similar nature for second and third pregnancies only. Since the rates of loss for these pregnancies are relatively low, the data eliminate the effect of order of pregnancy. Furthermore, additional information was provided by dividing the infant deaths and presenting the neonatal and postneonatal mortality rates separately.

In addition to the results shown here, the data in Table VIII and Fig. 8 show that *the increase in neonatal mortality is found mostly when the previous pregnancy terminated in a late fetal death and to a lesser extent in an infant death. The rate for postneonatal mortality increased only when the previous pregnancy terminated in an infant death.*

It appears, therefore, that these different components represent distinct and independent manifestations of reproductive wastage and suggest that different sets of causative factors may be responsible.

TABLE VIII. RATES BY OUTCOME OF THE IMMEDIATELY PRECEDING PREGNANCY FOR FETAL DEATHS UNDER AND OVER 20 WEEKS' GESTATION, AND FOR INFANT DEATHS UNDER AND OVER 1 MONTH OF AGE AS DETERMINED FROM THE PREVIOUS REPRODUCTIVE HISTORY OF *Mothers Under 50 Years of Age* ON THE ISLAND OF KAUAI, TERRITORY OF HAWAII, 1953.* *(Second and Third Pregnancies Only)*

OUTCOME OF IMMEDIATELY PRECEDING PREGNANCY	NUMBER OF LIVE BIRTHS AND FETAL DEATHS†	RATES FOR FETAL DEATHS		RATES FOR INFANT DEATHS	
		UNDER 20 WEEKS	20 OR MORE WEEKS	UNDER 1 MONTH	1-11 MONTHS
Live birth: survived first year	5,552	49.9	20.5	11.4	12.5
Live birth: died under 1 year of age	222	45.0	23.6	38.6	70.4
Fetal death at 20 or more weeks' gestation	152	59.2	69.9	67.7	16.1
Fetal death under 20 weeks' gestation	341	202.3	22.1	11.3	3.8

*See first footnote under Table II.

†Excludes 44 cases in which the immediately preceding pregnancy terminated in a multiple birth and 11 cases in which the outcome of the immediately preceding pregnancy was not reported.

Comment

The major findings in this study relate to a further refinement of knowledge concerning the familial tendency to repeated pregnancy losses. It is shown that this tendency is specific for the three components of loss: (1) early fetal, (2) late fetal and neonatal, and (3) postneonatal fatalities. This finding may contribute to our understanding of causal factors in reproductive wastage. The principal factors influencing the outcome of pregnancy may also fall into three categories: (1) those of a biological nature, including the genes and the maternal reproductive system, (2) obstetrical factors pertaining to labor and the birth process, and (3) external environmental factors. While both biological and environmental factors undoubtedly operate throughout the gestational cycle and their effects are not mutually exclusive, it appears that each has its own period of peak influence. Thus, the biological factors

seem to have greatest influence in determining the fate of the embryo and young fetus during the early weeks; obstetrical factors during the late fetal and neonatal periods (labor and delivery), and the influence of external environmental factors increases progressively with the age of the fetus and infant.

The findings of this study suggest that these three sets of factors operate independently of each other. This is evidenced by the fact that the rate of loss in one component (i.e., the early fetal group) is not increased when the previous loss was in another component, (i.e., late fetal or infant). The various components may, therefore, be thought of as representing three distinct manifestations of reproductive wastage. This finding also brings into focus the probable importance of the biological and genetic factors, especially in early fetal deaths. For it would be difficult to provide a satisfactory explanation for the *specificity* of the repetitive phenomenon on the basis of environmental influences alone.

In this connection attention may be called to the fact that the only specific form of loss which is affected by more than one form of previous loss is that of *neonatal mortality.* This rate shows an increase when the previous loss was either a *late fetal* or a *neonatal loss* (Fig. 8). This indicates that neonatal and late fetal mortality are affected by the same causal syndrome and behave similarly. This observation provides justification for the increasingly common practice of combining stillbirths and neonatal deaths into one category designated as *perinatal mortality.*

The findings with regard to order of pregnancy, age of mother, and interval between pregnancies seem to fit into specific patterns which serve to emphasize the probable relationships within the three major groups of causes.

Of equal value to the specific findings, is the fact that this method of retrospective study of reproductive wastage can provide reliable data. Longitudinal studies, important as they are, will undoubtedly be limited because of their inherent difficulties. The fact that it has been shown possible to elicit reliable information from women regarding their previous reproductive histories makes it feasible to coordinate the information thus derived with many factors and characteristics for more detailed and comprehensive investigations.

The study also suggests the value of complete and accurate reproductive histories of obstetric patients. Such data would provide information which could be studied in a method similar to that outlined in this paper, but more important, would furnish information of value in the care of the expectant mother. The repetitive characteristics, as pointed out in this study, are compelling arguments for physicians to pay special attention to the sequence of all previous pregnancies, their outcome, and the fate of the newborn infants. A simple statement as to the number of previous abortions and miscarriages is not sufficient to enable the physician to provide the best care for his patients.

The information could probably best be obtained by the physician himself. It is important to note, however, that a competent nurse can elecit reliable information from the mother regarding all her previous pregnancies.

Summary

This paper provides an analysis of the previous reproductive histories of all the women on the Island of Kauai, Territory of Hawaii, who had experienced at least one pregnancy. The data for the study were obtained from all women of childbearing age taken as part of a complete enumeration of the population of the island made in conjunction with a longitudinal study which is in progress. The data have been tested for all needed indices and found reliable when obtained from women who were less than 50 years of age. Consequently the analysis is based on the information obtained from this group of women. The following findings are recorded:

1. The results confirm other studies on the relatively high incidence of early fetal deaths. There were more than twice as many early as late fetal deaths.

2. The factors of order of pregnancy and age of the mother have somewhat different effects on the early fetal death rate, the late fetal and neonatal mortality rates, and the postneonatal death rates. The effect of order of pregnancy is stronger for the older infants, while the age of the mother exerts a greater influence on fetal mortality.

3. The interval between the termination of one pregnancy and the beginning of the next is associated with the survival of the offspring. The early fetal, late fetal, and neonatal mortality rates are high when the interval is short. They are at a minimum when the interval is around 2 years, and increase for longer intervals. On the other hand, postneonatal and childhood mortality rates are lower when the interval between pregnancies is longer.

4. There is a strong association between the outcome of one pregnancy and that of the immediately preceding one. When a mother suffers a loss in the form of a fetal or infant death, the chances are increased that she will sustain a subsequent loss. This association is specific for type of loss, i.e., when a woman has had an early fetal death she is more likely to have a similar accident in a subsequent pregnancy, but her chance of sustaining a late fetal loss is no greater than when the previous pregnancy resulted in a surviving infant. Similarly, if a women has sustained a previous loss through a late fetal death the likelihood of a similar accident is increased but the chance for an early fetal death in a subsequent pregnancy is not increased.

5. These findings are discussed in terms of possible etiological and causative factors. It is suggested that the three types of losses, (1) early fetal, (2) late fetal and neonatal, and (3) postneonatal mortality, represent three distinct manifestations of reproductive wastage, and are influenced by biological and environmental factors to different degrees and in different ways. Early fetal deaths are probably influenced most by unfavorable biological factors. Environmental factors become increasingly important as age increases.

6. The type of retrospective study described was found to be reliable and should provide a valuable method for further studies of reproductive wastage.

7. The specific repetitive character of reproductive wastage points to the value of complete and accurate reproductive histories as a means of increasing data available for study and for providing information of immediate value in the provision of care to pregnant women.

We wish to acknowledge our gratitude to Mr. Charles G. Bennett, Chief, Bureau of Health Statistics, Department of Health, Territory of Hawaii, for assistance in coding the data, to Miss Lucille Milkovich and Miss Helen E. Supplee, who have been extremely helpful in the statistical analysis, and to Miss Myrna G. Campbell, Supervising Nurse, and her staff of nurses on the Island of Kauai whose services have been indispensable. Most of all, we are indebted to the entire community residing on the Island of Kauai who are cooperating wholeheartedly in this study.

References

1. Baumgartner, Leona: Pediatrics **11**: 489, 1953.
2. Yerushalmy, J., and Bierman, Jessie M.: Obst. & Gynec. Surv. **7**: 1, 1952.
3. Greenhill, J. P.: J. Obst. & Gynaec. Brit. Emp. **54**: 577, 1947.
4. Nesbitt, Robert E. L., Jr., and Anderson, George W.: The Pathologic Aspects of Fetal Death in Utero, in Engle, Earl T., editor: Pregnancy Wastage, Springfield, Ill., 1953, Charles C Thomas, Publisher.
5. Davis, M. Edward, Potter, Edith L., and Bruce, William H.: Pertinent Factors in the Declining Perinatal Death Rate at the Chicago Lying-in Hospital, in Engle, Earl T., editor: Pregnancy Wastage, Springfield, Ill., 1953, Charles C Thomas, Publisher.
6. Potter, Edith L.: Pathology of the Fetus and the Newborn, Chicago, 1952, The Year Book Publishers, Inc.
7. Toverud, K. U., Stearns, G., and Macy, I. G.: Bulletin of the National Research Council No. 123, 1951.
8. Potter, Edith L.: Illinois M. J. **81**: 3, 1942.
9. Record, R. G., and McKeown, Thomas: Brit. J. Soc. Med. **3**: 183, 1949.
10. Baumgartner, Leona, Wallace, Helen M., Lansberg, E., and Pessin, Vivian: Am. J. Pub. Health **39**: 1549, 1949.
11. Yerushalmy, J.: Am. J. Hyg. **28**: 244, 1938.
12. Yerushalmy, J., Palmer, Carroll E., and Kramer, M.: Pub. Health Rep. **55**: 1195, 1940.
13. Sutherland, Ian: Stillbirths; Their Epidemiology and Social Significance, New York, 1949, Oxford University Press.
14. Gibson, J. R., and McKeown, Thomas: Brit. J. Soc. Med. **6**: 183, 1952.
15. Douglas, J. W. B.: J. Obst. & Gynaec. Brit. Emp. **57**: 143, 1950.
16. Rochester, A.: Children's Bureau Publication No. 119, Washington, 1923, U. S. Dept. of Labor.
17. Eastman, Nicholson J.: AM. J. OBST. & GYNEC. **47**: 445, 1944.
18. Yerushalmy, J.: Human Biol. **17**: 65, 1945.
19. Yerushalmy, J., Gardiner, E. M., and Palmer, C. E.: Pub. Health Rep. **56**: 1463, 1941.
20. Gardiner, E. M., and Yerushalmy, J.: Am. J. Hyg. **30**: 11, 1939.
21. Eastman, Nicholson J.: Habitual Abortion, in Meigs, J. V., and Sturgis, S. H., editors: Progress in Gynecology, New York, 1946, Grune and Stratton, Inc.
22. Schoeneck, F. J.: Obst. & Gynec. **1**: 610, 1953.
23. Baumgartner, Leona, and Erhardt, Carl: Some Observations on the Factors in the Incidence of Prematurity and Fetal Death, in Engle, Earl T., editor, Pregnancy Wastage, Springfield, Ill., 1953, Charles C Thomas, Publisher, p. 155.

MANAGEMENT OF VESICAL FISTULAS AFTER CESAREAN SECTION

H. C. FALK, M.D., AND M. L. TANCER, M.D., NEW YORK, N. Y.

(From the Obstetrical and Gynecological Service of Beth Israel Hospital)

VESICAL fistulas after cesarean section are infrequent. When they do occur, they fall into two distinct groups, each of which presents a characteristic clinical picture.

Vesicovaginocervical fistula: This lesion involves the cervix and vagina. It may be suspected early in the postoperative period because of the constant urinary leakage which occurs soon after removal of the indwelling catheter. Clinically this lesion resembles the classical vesicovaginal fistula with its distressing effects upon the patient's physical, social, and economic well-being.

Vesicocervical fistula: This lesion does not involve the vagina. There may or may not be urinary leakage early in the postoperative period. Leakage, if it does occur, will probably be incomplete and may diminish and almost completely disappear. As a result the patient may not be disturbed by incontinence of urine. Instead the patient may complain of an apparent amenorrhea associated with cyclic hematuria.

We have been able to find in the literature six cases of fistulas which followed cesarean section. We will review these and add three cases of our own.

CASE 1.—(Laffont and Ezes.[7]) A 32-year-old patient was seen two years after her fourth cesarean section, at which time the bladder was said to be dissected from the lower uterine segment with some difficulty as a result of the previous cesarean sections. She complained of amenorrhea since her last cesarean and gave a history of cyclic hematuria of three days' duration which occurred monthly since her fourth postoperative month. She was certain that urine was not lost per vaginam and that vaginal bleeding did not occur.

Methylene blue was instilled in her bladder and did not appear in the vagina. On hysterogram, the cervical canal was entered with ease. Dye entered the bladder and was subsequently voided. Dilatation and curettage performed on the twenty-third day after an episode of hematuria showed an endometrium with characteristic progesterone changes. The patient refused the recommended cytoscopy and operation.

CASE 2.—(Musset and Mazingarbe.[8]) The patient had a low cervical cesarean section with a longitudinal uterine incision. On the sixth postoperative day dysuria, pyuria, and a wound infection were simultaneously noted. Two months later the patient noted menstrual molimina and hematuria for four days, but no vaginal bleeding. This recurred twenty-eight days later. Cystoscopy revealed no bladder defect. At operation the bladder was transperitoneally dissected off the anterior uterine wall. An 0.8 cm. opening was found in the old uterine scar with a corresponding opening found in the bladder. Both openings were closed. The result was good.

CASE 3.—(Musset and Mazingarbe.) Following cesarean section the patient noted an absence of normal menstruation. Instead there was cyclic hematuria. There was no incontinence. A hysterogram showed dye in the bladder. Cystoscopy revealed no defect but only a depression at six o'clock behind the trigone. Operation was refused.

CASE 4.—(Stening.[10]) A 26-year-old patient was in labor for four days after which forceps delivery was attempted and failed. Bloody urine was noted at this time. A low cervical cesarean section was then performed. On the seventh postoperative day all urine passed per vaginam. By the third postoperative week the patient was almost completely continent. By the eighth postoperative month cyclic hematuria and only occasional, partial urinary leakage were noted. A transperitoneal approach to the fistulous tract failed and the patient retained her symptoms for the next ten years at which time unrelated pelvic symptoms (not described by Stening) caused her to seek relief. On pelvic examination there was noted a slight trickle of urine from the external cervical os. (Other findings not given by Stening.) Intravenous pyelography and cystoscopy were performed. (Findings not given by Stening.)

An abdominal total hysterectomy, left salpingo-oophorectomy, and appendectomy were performed to cure the primary pathology. (Pathology not described by Stening.) The bladder opening was then closed and covered by a layer of cervicovaginal fascia. The result was good at six months.

CASE 5.—(Bourgeois.[3]) A 25-year-old patient was delivered by extraperitoneal cesarean section during which the bladder had been inadvertently opened and subsequently repaired. The patient would not tolerate an indwelling catheter and vaginal leakage of urine was noted in the early puerperium.

At urological examination, the opening was seen just above the left ureteral orifice. Urine was seen coming from the uterus.

An extraperitoneal transvesical and paravesical abdominal approach with suprapubic drainage were carried out. After the bladder was opened, it was found that the bladder and underlying "uterus" could not be mobilized, and a left paravesical approach was used. After closure of the "uterine" opening, the bladder muscle, and perivesical fascia, the bladder mucosa was closed transvesically. At one month after operation the results were good.

CASE 6.—(Aschner.[1, 2]) A 44-year-old patient had noted absence of urinary control on standing following a cesarean section performed twenty-two years previously. Symptoms progressed until one year after the menopause when all control was lost. Indigo carmine placed in the bladder came out of the external os. Radiopaque dye placed in the bladder allowed visualization of the uterus and tubes. Cystoscopy showed a defect on the posterior bladder wall.

At operation the abdomen was opened transperitoneally and the bladder approached retroperitoneally. Defects in the bladder and cervix were repaired. The postoperative course was stormy and included the following complications: paralytic ileus, pelvic cellulitis, thrombophlebitis of the pelvic veins, pulmonary infarctions, wound dehiscence, and incisional hernia. After seven years urination was normal.

CASE 7.—Z. B., Beth Israel Hospital No. 256904. (H. C. F.) A 52-year-old patient was delivered by cesarean section nineteen years previously. Following section she noted an absence of menstruation and cyclic hematuria but no leakage of urine. Six months prior to this admission the periods of hematuria began to last seven to ten days, and were associated with the passage from the bladder of clots which caused pain and dysuria. On pelvic examination a diagnosis of myomas of the uterus was made. Cystoscopy showed the upper urinary tract and bladder mucosa to be normal. There was a vesicocervical fistula just above the interureteric ridge (Fig. 1).

An abdominal total hysterectomy and bilateral salpingo-oophorectomy were performed for the primary pathology. After section of the fistulous tract (during the hysterectomy), the defect in the bladder was closed transversely in two inverting layers. The pubocervical fascia was then used to cover the suture line (Fig. 2). The vault of the vagina was not closed. The posterior peritoneum was sutured to the vesical peritoneum above the bladder repair.

The pathological examination (No. 708901) was made by Dr. William Antopol. The specimen consisted of a uterus measuring 12 cm. from the fundus to the external os, 6 cm. across the fundus, and 5 cm. anteroposteriorly. The uterus and uterine cavity were distorted by intramural and subserous firm, encapsulated nodules. The largest of these was located in the fundus submucosally, consisting of gray-white fibers in whorled arrangement. The endometrium was smooth and hemorrhagic, measuring up to 0.2 cm. in thickness. The cervix measured 2 cm. in diameter at the level of the external os. The cervical canal was 3.5 cm. long. On the anterior wall of the cervix there was a 1.6 cm. defect, the distal edge of which was 2 cm. from the external os. The defect was lined by gray hemorrhagic tissue, communicated with the cervical canal, and extended to the internal os which was narrowed.

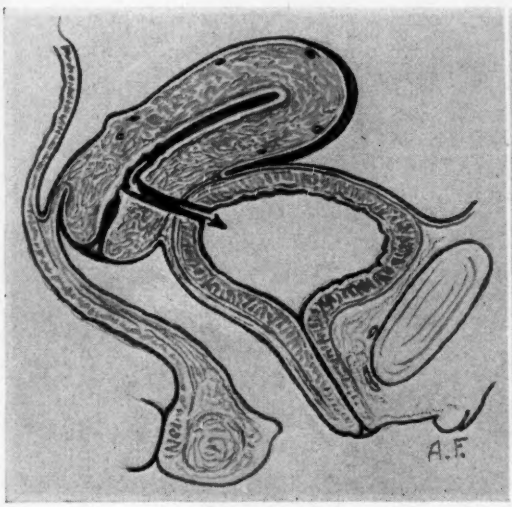


Fig. 1.

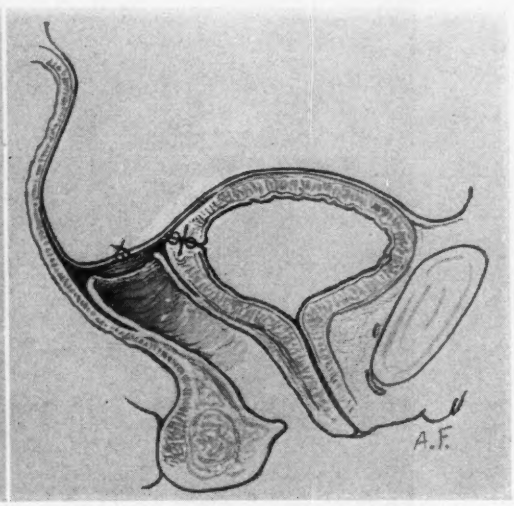


Fig. 2.

Fig. 1.—Vesicocervical fistula. Path of menstrual flow.
Fig. 2.—Bladder defect repaired after total hysterectomy.

Fig. 3 shows the anterior surface of the removed uterus and cervix. A probe passes through the external os, the cervical canal, and the internal os. The probe may be seen through the cervical defect.

Fig. 4 shows the submucous myoma in the bisected fundus uteri.

Fig. 5 is a close-up of the cervix opened longitudinally on the anterior surface. Arrows point to the fistula defect (*A*), and the narrowed internal os (*B*).

Postoperatively a Foley catheter was left in situ for seven days. Upon its removal the patient voided spontaneously without residual urine and the vagina remained dry. Follow-up at six months showed a good result.

Case 8.—C. S. (Operated upon by H. C. F. at Haifa Hospital, Israel, March, 1952.) A 32-year-old patient was delivered by cesarean section after three days of labor. A longitudinal incision in the lower segment was used. On the tenth postoperative day urinary leakage occurred and persisted until repair.

Pelvic examination showed a healed anterior vaginal vault scar. The anterior lip of the cervix had a longitudinal split and the apex of this laceration and of the vaginal scar coincided. At this point a probe could be introduced via a fistulous tract into the bladder.

At operation, after hemicircumcision of the cervix, the bladder was dissected from the anterior cervical wall for a distance of 1.5 cm. above the fistulous tract. The edges of the cervical laceration were freshened and the cervix reconstructed. The bladder was then repaired in two layers with interrupted inverting sutures along a transverse line with the

Fig 3.

Fig. 4.

Fig. 5.

Fig. 3.—Anterior view of uterus. Probe seen through cervical defect.
Fig. 4.—Submucous myoma in bisected fundus uteri.
Fig. 5.—Close-up of cervix opened longitudinally. *A*, Fistula defect. *B*, Narrow internal os.

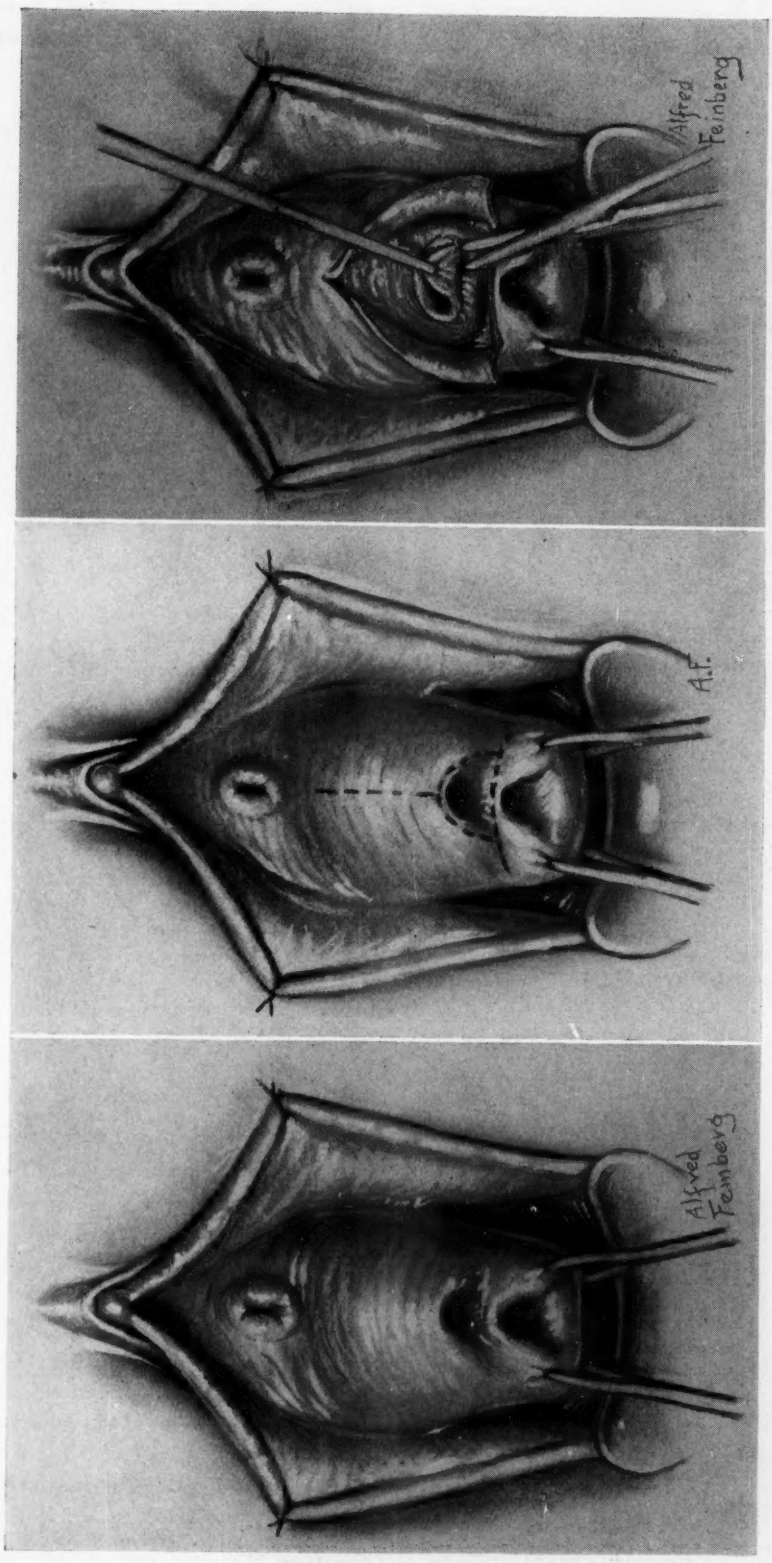


Fig. 6.

Fig. 7.

Fig. 8.

Figs. 6-13.—Vesicovaginocervical fistulas.
Fig. 6.—The lesion at time of operation.
Fig. 7.—Proposed line of incision.
Fig. 8.—Fistula mobilized.

use of No. 00 chromic catgut. The bladder suture line was then sutured to the anterior cervical wall above the repaired cervical laceration. The vaginal mucosa was then resutured. At no time was the peritoneum opened.

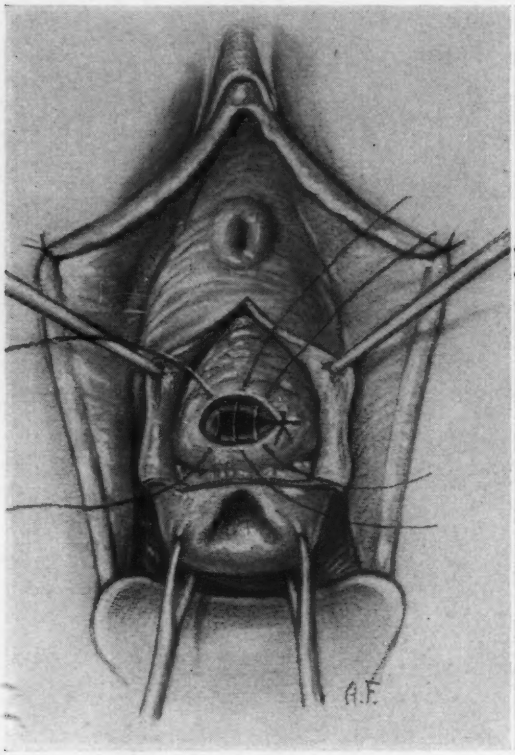


Fig. 9.

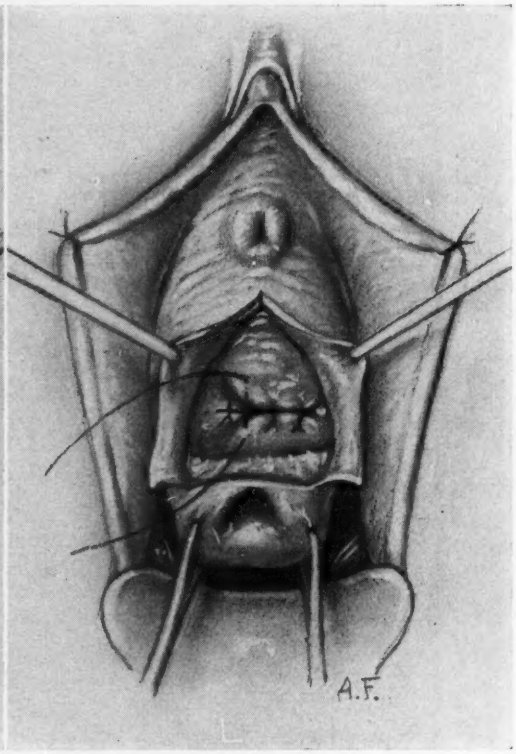


Fig. 10.

Fig. 9.—Transverse closure. First suture layer.
Fig. 10.—Second suture layer.

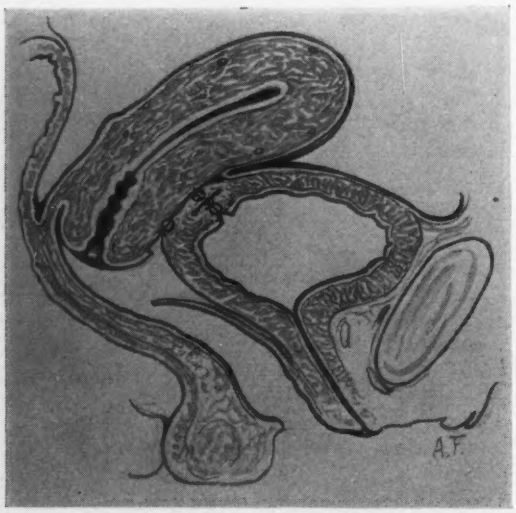


Fig. 11.—Lateral view. The bladder repair is sutured to the anterior cervical wall.

An indwelling catheter was left in place and removed after forty-eight hours at which time the vagina was dry. One year postoperatively there was normal bladder function.

CASE 9.—S. H., Beth Israel Hospital No. 267409. (H. C. F.) During a cesarean section for frank breech with a large baby in a 30-year-old primigravida, a longitudinal incision was made in the lower uterine segment and the bladder was injured. The injury was immediately repaired and an indwelling catheter was left in the bladder. Upon removal of the catheter on the twelfth postoperative day, constant urinary leakage ensued and continued until the defect was repaired nine months later.

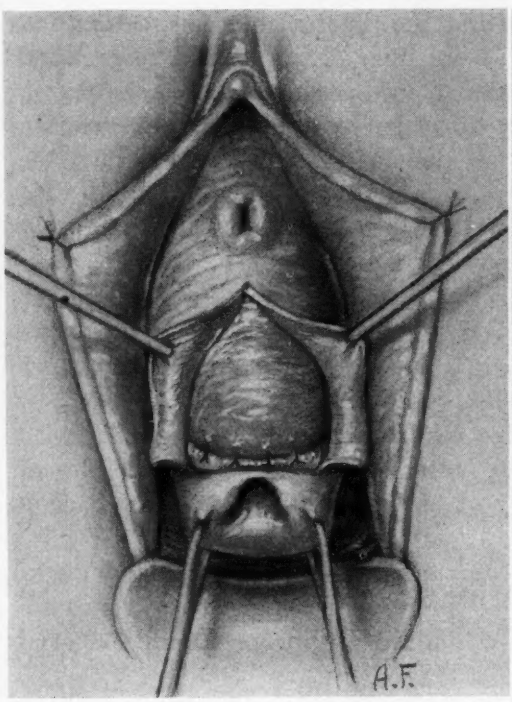


Fig. 12.

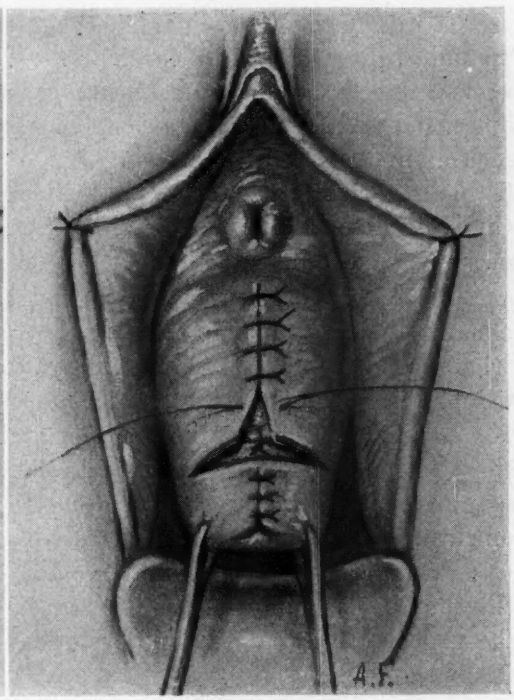


Fig. 13.

Fig. 12.—Bladder repair sutured to anterior cervical wall.
Fig. 13.—After freshening the cervical laceration, a new cervical os is constitued and vaginal mucosa reunited.

Cystoscopy showed a large defect just above the mid-trigone with the ureteral orifices 1 cm. lateral to the defect.

Pelvic examination showed a cervix in which the anterior lip was split longitudinally, and at the point where the vagina and the cervical laceration met, a finger could be inserted into the bladder (Fig. 6).

At operation the vaginal mucosa was separated widely from the underlying bladder and the bladder mobilized from the cervix (Figs. 7 and 8). The defect in the bladder was closed transversely using two layers of inverting, interrupted, No. 00 chromic catgut sutures (Figs. 9 and 10). The bladder was then sutured to the anterior cervical wall (Figs. 11 and 12). The edges of the cervical laceration were then freshened and the cervix was reconstructed (Fig. 13). The vaginal mucosa was then reunited. At no time was peritoneum opened. The result six months postoperatively was normal continence.

Comment

Cases 8 and 9 are vesicovaginocervical fistulas. The injury appears to occur when the longitudinal incision in the lower uterine segment is inadvertently extended downward to involve the bladder. Unless the lower end of this incision is made under vision with the bladder well retracted, this lesion may result. Extension of a well-placed longitudinal incision involving the bladder may also occur during delivery of the fetus. Upon removal of the indwelling catheter constant urinary leakage, such as occurs in the classical vesicovaginal fistula, should suggest the presence of this lesion.

If injury to the bladder is recognized at the time of cesarean section, immediate repair should be carried out. The bladder defect should be repaired in two layers and an indwelling catheter placed. Should this repair fail, operation should be postponed from nine to twelve months following cesarean section in order to allow sloughing of all damaged tissue and to allow the fistula sufficient time to delineate itself. This period of time will allow for complete involution of pelvic tissues as well. Operations performed too early may result in failure due to poor healing of subinvoluted tissues.

Prior to operation it is essential that a complete urological work-up be performed so as to know exactly the relationship of the fistulous tract to the trigone and ureters. It is important for a good result to have normal upper urinary tracts and normal bladder mucosa at the time of operation.

Repair of vesicovaginocervical fistulas can be accomplished vaginally with the assistance of a Schuchardt incision if necessary. The basic principles of fistula repair, namely, complete mobility of bladder wall and lack of tension on suture lines, cannot be overstressed.

Postoperative care should include constant drainage of the bladder and this may be accomplished by using an indwelling Foley catheter passed through the urethra or by suprapubic cystotomy if desired. Appropriate antibacterial drugs should be used.

Cases 1 through 7 represent vesicocervical fistulas. All except Cases 5 and 6 conform to a pattern. Cesarean section was followed by apparent amenorrhea and vesical menstruation. In Cases 1, 2, 3, and 7 there was no urinary leakage. In Case 4, urinary leakage was temporary and incomplete. The patients in this group appeared to live comfortably despite the presence of the defect. Two of these patients refused operation and two others deferred therapy until operation for completely divorced pelvic pathology was found necessary ten and nineteen years after the occurrence of the fistulas. At these times, the fistulas were repaired as coincidental procedures.

Complete urological work-up is essential prior to surgery for the reasons previously stated under vesicovaginocervical fistulas. Hysterography might also be performed to demonstrate patency of the cervix and the fistulous tract.

It is of interest to speculate on the reasons why urine does not flow from the bladder through the fistulous tract and hence out of the patent cervix. One must wonder, too, why the menstrual discharge flows into the bladder but not through a patent cervical canal. Laffant and Ezes conjectured that a

valve mechanism of some sort exists. In Case 7 no such mechanism could be demonstrated. However Fig. 5 illustrates the pathologist's description that the fistulous tract seems to extend upward from the bladder to the internal os.

Case 5 had constant urinary leakage and no amenorrhea and, from the symptoms, this case resembled a classical vesicovaginal fistula. In Case 6 the author does not mention the menstrual cycle, type of urinary leakage, or the time element between cesarean section and repair, so that it is difficult to assess these factors. This same author (Bourgeois) also reports another case of fistula which occurred following extraperitoneal cesarean section. No description of the lesion is given, however, and spontaneous cure resulted after reinsertion of an indwelling catheter for ten days. He mentions still another case of fistula following extraperitoneal cesarean section but no details are given so that neither case was included in the series.

If surgery is to be performed to cure a vesicocervical fistula, various approaches may be used. If associated pelvic surgery is performed and the uterus removed, as in Cases 4 and 7, the repair of the bladder defect should follow removal of the uterus at which time the vault of the vagina is to be left open.[5] Should this repair fail, a vesicovaginal fistula will occur and secondary repair is relatively simple through a vaginal approach as described by Falk and Bunkin,[6] using the Latzko partial colpocleisis. The results with the latter procedure are uniformly good. Fig. 2 shows the bladder repaired after removal of a pathological uterus.

If operation is to be performed while the uterus remains in place, one may use a transperitoneal approach as in Case 2.

While the authors did not describe the technique in detail, it is presumed that a method similar to that of von Dittel[4] was used.

Bourgeois prefers the extraperitoneal, transvesical approach of Phaneuf and Graves[9] which he was forced to modify in Case 6. Bladder mobility could not be obtained and it was necessary to approach the fistula from the left paravesical space. This would seem to jeopardize the ureter unnecessarily, despite the implied advantage of not entering the peritoneal cavity as in the von Dittel approach. The antibacterial agents available today minimize the danger from peritonitis. This should diminish the need for an extraperitoneal approach with its concomitant danger to the ureter.

Aschner's extraperitoneal approach to the bladder after entering the peritoneal cavity appears to be unnecessary.

Summary

1. Six cases of vesical fistulas which occurred after cesarean section found in the literature are reviewed and three are added.

2. Of these, two are vesicovaginocervical fistulas and seven are vesicocervical fistulas.

3. Vesicovaginocervical fistulas are best treated in the fashion acceptable for the classical vesicovaginal fistula.

4. Vesicocervical fistulas which occur after cesarean section may fit a clinical pattern of apparent amenorrhea, cyclic hematuria, and absence of urinary leakage via the vagina.

5. Various methods for the surgical repair of these lesions are discussed.

References

1. Aschner, P.: J. Urol. 69: 774, 1953.
2. Aschner, P.: Personal communication.
3. Bourgeois, G. A.: Am. J. Surg. 83: 671, 1952.
4. von Dittel, L.: Wien. Klin. Wchnschr. 25: 449, 1893.
5. Falk, H. C.: Harlem Hosp. Bull. 3: 89, 1950.
6. Falk, H. C., and Bunkin, I. A.: Surg., Gynec. & Obst. 93: 404, 1951.
7. Laffont, A., and Ezes, H.: Gynéc. et obst. 46: 248, 1947.
8. Musset, R., and Mazingarbe, A.: Presse. méd. 58: 763, 1950.
9. Phaneuf, L. E., and Graves, R. C.: Surg., Gynec. & Obst. 88: 155, 1949.
10. Stening, M. J. L.: M. J. Australia 1: 12, 1950.

FLICKER PHOTOMETRY AND TOXEMIA OF PREGNANCY

FREDERICK L. PERL, M.D., AND ARNOLD OPER,* BROOKLYN, N. Y.

(From the State University of New York College of Medicine at New York City, Department of Obstetrics and Gynecology of Kings County Hospital, and the Faculty of Pure Sciences at Columbia University)

RECENT studies with the Krasno-Ivy[3] flicker photometer by Brill and associates[1, 2] and Marty and Hardy[8] have been highly encouraging in regard to the recognition of incipient toxemia of pregnancy. Any method which offers a possibility of predicting, with a reasonable degree of surety, which particular patient will develop a toxemia of pregnancy should be thoroughly studied. The present study was initiated to answer certain specific questions, namely:

1. Is this a reliable test for the preclinical recognition of toxemia of pregnancy?
2. Can this test be used as a guide for the prognosis of a clinically diagnosed case of toxemia of pregnancy, and can methods of treatment of this disease be thereby evaluated?
3. What is a statistically valid method for determining flicker fusion threshold (FFT)?
4. Can this test distinguish chronic hypertensive disease, with or without superimposed acute toxemia, from true pre-eclampsia?
5. Is the flicker fusion threshold correlated with any other factors, such as hemoglobin, blood pressure, weight gain, or parity?
6. Can vasospasm be demonstrated ophthalmologically in patients with a positive test?

History and Physiology

A flickering source of light will be perceived as such by the eye until the frequency of the flickering becomes so rapid that the eye perceives only a steady light; that is, when the duration of the "after image" of the individual stimulus is greater than the interval between stimuli. This is called the flicker fusion threshold, or FFT. The FFT is a variable point, readily changed by such things as intensity of the light, color of the light, smoking, drugs, dark adaptation of the eye, mental attitude of the patient, and many others. Many of these variables can be held constant during any specific test, thereby obtaining an accurate FFT. Numerous workers have shown that fatigue,[4] hypoxia,[5] and mental states[6] alter the FFT. The work of Krasno and Ivy[3] has stimulated the use of the flicker photometer† in pregnancy. These workers have postulated that certain organic vascular diseases are preceded by a chronic state of vasospasm which can be relieved by the administration of sublingual nitro-

*The statistical data in this paper are abstracted in a Master's Thesis by A. O. at Columbia University.

†The Flicker Photometers used in this study were supplied by the American Hospital Supply Company, Chicago, Ill.

glycerine, thereby increasing the FFT by improving retinal blood supply. Their work tends to support this hypothesis. This is then carried into pregnancy by further assumptions that clinically recognizable toxemia of pregnancy is also preceded by chronic vasopasm.[1, 2] The basis for the test is a significant change in the FFT following the administration of sublingual nitroglycerine. If vasospasm is present, administration of nitroglycerine will increase the blood supply to the retina by vasodilatation, thereby raising the FFT. This is called a "positive test." If, however, there is no vasospasm, then the administration of nitroglycerine will cause a passive hyperemia of the retina and decrease the FFT. This is a "negative test." If there is no change in the FFT after the administration of nitroglycerine, a second tablet is given and the test repeated. If there is still no change, then a state of severe vasospasm, unrelieved by nitroglycerine, is assumed and the test considered positive.

Recent studies by Rugart,[7] Roddick and Benaron,[9] Gillim,[10] and Morris and co-workers[11] have failed to support the theory postulated by Krasno and Ivy[3] and applied to toxemia of pregnancy by Brill.[1, 2]

Material

All patients were selected from the Out-Patient Department or wards of the Department of Obstetrics and Gynecology, Kings County Hospital, Brooklyn. The student nurses were selected from the School for Nurses Training of Kings County Hospital.

Method

The method of conducting the test is relatively simple and requires about 20 to 30 minutes to obtain a set of readings during any one visit. The patient is instructed to refrain from smoking and taking drugs or alcohol during the twelve-hour period preceding the test. A ten-minute rest period is used prior to the test to allow accommodation for the light in the room. The patient is instructed in the use of the machine and to push the button as soon as the light begins to flicker. The patient is allowed two or three trial runs to become acquainted with the machine. The first three readings obtained thereafter are averaged and taken as the "base line" FFT. One tablet of nitroglycerine, grain 1/150, is given sublingually, and after two minutes the set of three readings is repeated twice at two-minute intervals. The effect of the nitroglycerine is noted by the usual symptoms of flushing of the face, palpitation, temporal pulsation, and frequent transitory headache. Although a change of plus or minus 60 cycles per minute is recommended as a significant change following the administration of nitroglycerine,[1, 2] we used a change of 42 cycles per minute, because this was statistically determined to be accurate 95 per cent of the time. (See results of Experiment 1.) If no change is noted, a second tablet of nitroglycerine is given and the readings repeated. After all readings are tabulated and averaged, the pre- and post-nitroglycerine thresholds are determined and the change in the FFT computed. The test is then noted as positive or negative.

Experimental Design

Because of the realization that most experiments include unavoidable variables, it was decided to run three separate experiments. Each would in-

clude known variables that were impossible to eliminate; but by statistical analysis valid interpretations could be drawn from the combined study.

Experiment 1 was conducted with a random sample of 18 freshman student nurses, which comprised Group A. The experiment was designed to give us statistically reliable information as to what to call a valid change in the FFT, either positive or negative. This valid change is then used in later experiments. (See results of Experiment 1).

Experiment 2 was conducted on all pregnant women registered by Jan. 1, 1953, in the Out-Patient Department at Kings County Hospital, Brooklyn, New York, Service of the State University of New York (at New York) whose expected dates of confinement were between March 15, and April 15, 1953. This group of patients comprised Group B and totaled 66 patients. They were chosen so that they could be studied throughout the third trimester of their pregnancies, when toxemia becomes manifest. This sample has some bias which does not affect the validity of the test, but may influence the occurrence of toxemia. The patients were tested during their routine obstetrical visits, in the immediate puerperium, and at their visit six weeks post partum. The observers who made the readings knew nothing about their pregnancies or previous histories. A total of four observers were used and these were interchanged between patients.

Experiment 3 was conducted on a group of ward patients with the clinical diagnosis of toxemia of pregnancy of one type or another. This group, labeled C, totaled 12 patients. Since all of these patients had toxemia we expected them to give consistently positive responses prior to delivery, and to revert to a negative response during the postpartum period unless permanent vascular damage were present, either as chronic hypertensive disease or as a residuum of acute pre-eclamptic toxemia. These patients were tested frequently during their antepartum and postpartum hospital stays and at their visits six weeks post partum.

Results

Experiment 1.—

In the literature to date numerous investigators have used different variations in FFT as significant, without regard to normal individual variation. This experiment was designed (by one of us, A. O., a statistician) to eliminate as many variables as possible and to measure intra-individual variation. A balanced-design experiment was constructed so that by applying the method of Analysis of Variance, a true measure of average variation within an individual could be determined. The experiment not only sought to eliminate but also estimated variations caused by time, currents, order, machines, etc.

The design required three sets of three readings each, using each machine and operator in accordance with defined instructions. Means (averages) of the sets of three readings were then analyzed as to the variation within an individual. The analysis of the average of three readings was done because in later experiments a change in the average before and after nitroglycerine was to be interpreted as a positive or negative response.

The analysis of the data collected on the patients comprising Group A showed a mean variation of 16.67 cycles per minute within an individual. It was decided that a 95 per cent level of accuracy was desired. Since individuals fluctuate in the amount that they vary, the expected error in defining a test as positive or negative would be less than 5 per cent (error of the first kind). In order to attain this accuracy we took 2.5 times the mean variation (16.67 cycles per minute), or 42 cycles per minute, as a significant change in FFT. Since a test in which no change in the FFT was observed or one in which the change was minimal after repeated administration of nitroglycerine was to be considered positive, errors of the second kind need not be appraised.

In subsequent experiments, although any change greater than 42 cycles per minute was considered significant, almost all changes were in the range of 70 to 100 cycles per minute. This was equally true when either positive or negative responses were obtained.

This experiment also showed that light, time of day, operator, and machine did not alter the results of the test significantly.

Experiments 2 and 3.—

The patients in Group B totaled 66 patients upon whom a total of 184 readings were made (an average of 2.8 readings per patient). A total of 12 patients comprised Group C upon whom a total of 78 readings were made (an average of 6.5 readings per patient). Analysis of Groups B and C, a total of 78 patients, upon whom 262 readings were recorded (an average of 3.4 readings per patient), shows that in only 35 out of 75 patients (3 invalid), or 46.7 per cent of the patients, were the predictions correct, less than could be done by chance. These data are set forth in Table I.

TABLE I. RESULTS OF PREDICTIONS

	GROUP B	GROUP C	TOTAL	PERCENTAGE	TOTAL	AV. READING PER PATIENT
True positives	3	4	7	9.3	46.7	4.9
True negatives	28	0	28	37.4		3.0
False positives	27	0	27	36.0	53.3	2.3
False negatives	6	7	13	17.3		4.1
Invalid	2*	1*				

*Patients who did not cooperate or mechanical difficulty.

In Group C, patients hospitalized because of clinical toxemia of pregnancy, the FFT accorded with the hypothesis in only 4 out of 11 patients, or 36.4 per cent, in spite of an average of 6.5 readings per patient. In both groups, separate analyses revealed correct results in less than 50 per cent of tests.

In order to see if the test would be more reliable if more readings were taken per individual, Table II was made. It will be noted that the ability of the test to predict the future development of toxemia improves, but not sufficiently, as the results are still only 60 per cent correct, in the best cases.

TABLE II. DISTRIBUTION OF PREDICTIONS ACCORDING TO NUMBER OF READINGS PER INDIVIDUAL

NO. READINGS PER PATIENT	PREDICTIONS				PERCENTAGE CORRECT
	NO. CORRECT	NO. FALSE	NO. INVALID	TOTAL	
1	5	10	1	16	33.3
2	8	13	0	21	38.1
3	8	6	1	15	57.1
4	4	3	1	8	57.1
5	6	4	0	10	60.0
Over 6	4	4	0	8	50.0
Total	35	40	3	78	46.7

In Group B, 30 patients had positive tests but only 3, or 10 per cent, developed toxemia; whereas, of 34 patients with negative tests, 6, or 17.6 per cent, developed toxemia. In this random sample, 9 out of 66 patients, or 14.1 per cent, developed toxemia, as compared to 194 out of 2,167 patients in the general clinic population, i.e., 9 per cent. This difference is easily accounted for by chance. Six of the 9 patients who developed toxemia, or 67 per cent, never had a positive test. It necessarily must be concluded that the test for measuring a change in the FFT after the administration of nitroglycerine, as previously defined, is totally unreliable in predicting which patient will develop toxemia of pregnancy.

An attempt was made to obtain postpartum readings on all patients in these two groups, but only 53 patients of the 78 returned for their postpartum visits. Table III records the results obtained from one week to three months post partum. Of the 58 patients who never developed signs of toxemia of pregnancy, 27 had positive antepartum tests. Seventeen of the patients in this latter group were seen post partum. Six remained positive, although no signs of chronic disease could be found. Analysis of patients with pre-eclamptic toxemia and chronic hypertensive disease, with or without superimposed acute toxemia, gave variable results and no conclusions could be drawn.

TABLE III. DISTRIBUTION OF PREDICTIONS ACCORDING TO POSTPARTUM READINGS

POST-PARTUM RESULTS	PREDICTIONS												
	WITHOUT TOXEMIA (-)				PRE-ECLAMPSIA				HYPERTENSION + TOXEMIA			HYPERTENSION -TOX.	TOTAL
	FALSE POS.	NEG.	INV.	TOT.	FALSE NEG.	POS.	INV.	TOT.	FALSE NEG.	POS.	TOT.	FALSE NEG.	
Positive	6	0	0	6	1	3	1	5	2	1	3	1	15
Negative	11	16	1	28	2	2	0	4	2	0	2	1	35
No. post-partum reading	10	13	1	24	3	0	0	3	1	0	1	0	28
Total	27	29	2	*58*	6	5	1	*12*	5	1	*6*	*2*	*78*

Comment

The determination of the flicker fusion threshold before and after the administration of sublingual nitroglycerine was found to be an unsatisfactory method for the preclinical recognition of toxemia of pregnancy. Only 10 per cent of 30 patients with positive tests later developed toxemia of pregnancy, while 17.6 per cent of 34 patients with negative tests subsequently developed toxemia. If the assumption that vasospasm can be relieved by nitroglycerine administered sublingually, thereby increasing the FFT, is correct, then patients who have already developed toxemia should show a consistently positive response. Only 36.4 per cent of our patients in Group C supported this hypothesis. During the hospital stay of the patients in Group C the test varied tremendously in 73.6 per cent, but the results could in no way be correlated with a decrease or increase in the severity of the disease. In addition, vasospasm should be readily evident in the patient with moderately severe toxemia. Vasospasm was noted in the eyegrounds in these patients, but with an equal frequency between patients who showed positive and negative responses. Thus, the response to the test in clinical cases of vasospasm does not support the hypothesis upon which the test for flicker fusion threshold is based. No statistically significant correlation could be found between flicker fusion threshold and hemoglobin values, weight gain during pregnancy, age or parity of the patients.

It was readily apparent during the conduct of the test that the patients exhibited a marked learning potential, which decreased the validity of the test. There was no accurate way, however, that this ability to learn could be assessed. Patients who were obviously emotionally labile showed marked variations between readings, so as to make it difficult to evaluate results.

Summary and Conclusions

The results obtained are similar to those of several other investigations and fail to support the hypothesis postulated by Krasno, Ivy, and Brill and his collaborators that toxemia of pregnancy is preceded by a period of vasospasm which can be detected by determining the pre- and post-nitroglycerine flicker fusion thresholds. We have concluded the following:

1. The test for the change in FFT after the administration of nitroglycerin is totally unreliable in predicting which patient will develop toxemia of pregnancy.

2. The FFT test cannot be used to evaluate the course of a clinically manifest case of toxemia of pregnancy.

3. A change in FFT after administration of nitroglycerine of 42 cycles per minute is statistically significant 95 per cent of the time.

4. Chronic hypertensive disease, with or without superimposed toxemia, cannot be distinguished from acute toxemia of pregnancy, that is, pre-eclampsia, by using the FFT test.

5. There is no significant correlation between hemoglobin values, weight gain during pregnancy, age and parity of the patient, and FFT.

6. Vasospasm, as determined by ophthalmological examination, was present in patients with toxemia of pregnancy to an equal degree in those who had positive or negative tests.

References

1. Brill, H. M., Golden, M. J., Woolf, H. L., Klawans, A. H., and Long, J. S.: Am. J. Obst. & Gynec. 62: 614, 1951.
2. Brill, H. M., Long, J. S., Klawans, A. H., Golden, M. J., and Seaman I.: Am. J. Obst. & Gynec. 64: 1201, 1952.
3. Krasno, L. R., and Ivy, A. C.: Circulation 1: 1267, 1950.
4. Simonson, E., and Enzer, N.: J. Indust. Hyg. & Toxicol. 23: 83, 1941.
5. McFarland, R. A., Halperin, M. H., and Ninen, J. I.: Am. J. Physiol. 144: 378, 1945.
6. Krugman, H. E.: Psychosom. Med. 9: 269, 1947.
7. Rugart, Karl F.: Obst. & Gynec. 1: 564, 1953.
8. Marty, J. P., and Hardy, J. A.: Am. J. Obst. & Gynec. 64: 1149, 1952.
9. Roddick, J. W., and Benaron, H. B.: Obst. & Gynec. 4: 260, 1954.
10. Gillim, D. L.: Obst. & Gynec. 4: 264, 1954.
11. Morris, N., Tomkinson, J. I., and O'Connor, B. J.: J. Obst. & Gynaec. Brit. Emp. 60: 680, 1953.

THE USE OF SULFISOXAZOLE* CREAM IN THE POSTPARTUM PATIENT

PAUL A. BISCHOFF, LIEUTENANT COLONEL, MC, USA, KENT P. UPCHURCH, MAJOR, MC, USA, AND JOHN J. CARTER, CAPTAIN, MC, USA

(From the Department of Obstetrics and Gynecology, Tripler Army Hospital, Honolulu, Territory of Hawaii)

THE prevention of cervical and vaginal disease resulting from pregnancy and parturition is one of the major goals of modern obstetrics. Careful vaginal examination and treatment of vaginal or cervical disease are indicated during pregnancy, examination of the cervix and vagina immediately post partum, and repair of any damage done in parturition have become the standard technique in all well-run obstetrical clinics and hospitals. Very little attention, however, has been given to prophylaxis during the postpartum period.

Physiological and anatomical changes which occur during pregnancy and immediately after delivery predispose to vaginal and cervical disease. Change in the vaginal flora associated with alterations in vaginal pH, hyperemia and edema of the cervix, invasion of the vagina and cervix by pathogenic organisms, all play a significant part in the occurrence of postpartum vaginitis and cervicitis. The purpose of this study was to determine whether the use of an antibacterial vaginal cream would significantly alter the incidence of postpartum vaginitis and cervicitis. The material† used for this purpose was a 10 per cent suspension of sulfisoxazole in a water-soluble vanishing cream base. This preparation had previously undergone in vitro and animal studies which showed that it possesses a wide antibacterial spectrum and produces little allergic sensitivity.

The case material included in this study consisted of 300 multiparas who had been delivered at or near term and in all of whom an episiotomy had been performed. In none of these women had there been any significant complications either during pregnancy or at the time of delivery. The cases were divided into two groups. Alternating patients were given a 3 ounce tube of sulfisoxazole cream equipped with a vaginal applicator. They were instructed to apply one applicatorful of the preparation, nightly, initiating treatment on the seventh postpartum day and continuing it until the supply was exhausted, a period of approximately two to three weeks of treatment. In the other half of the patients who served as controls, no medication was employed. All patients were instructed not to use douches and to refrain from intercourse until after re-evaluation in the sixth postpartum week. At that time a gynecological examination was made in every patient. Table I shows the

*Sulfisoxazole is the generic designation for 3, 4-dimethyl-5-sulfanilamido-isoxazole, available as Gantrisin.

†The Gantrisin (sulfisoxazole) Cream, 10 per cent, used in this study was supplied through the courtesy of Dr. S. Evert Svenson, Hoffmann-La Roche, Inc., Nutley, N. J.

frequency of cervical and vaginal pathology encountered in the two groups. As is seen, the incidence of abnormal findings was 20 per cent in the treated group and 38.6 per cent in the untreated controls.

TABLE I. INCIDENCE OF DISEASE ENCOUNTERED IN 300 CASES AT THE END OF THE SIX-WEEK PERIOD

	TOTAL NO. OF PATIENTS	NO. OF PATIENTS WITH DISEASE	NO. OF PATIENTS WITHOUT DISEASE	PER CENT DISEASED
Treated	150	30	120	20
Control	150	58	92	38.6

Thus, the occurrence of cervical and vaginal disease in the latter group was approximately twice that found in the former group.

Table II shows the types of disease encountered at the end of the six-week period in the 300 patients studied. In several cases more than one pathological entity was found. With the exception of the simultaneous occurrence of erosion and ectropion, recorded only under erosion, each pathological finding in a given patient was listed separately.

TABLE II. TYPES OF DISEASE* ENCOUNTERED IN 150 TREATED AND 150 CONTROL CASES AT THE END OF THE SIX-WEEK PERIOD

	CONTROL CASES (58)	THERAPY CASES (30)
Vaginitis		
Trichomonas vaginalis	2	0
Monilial	1	0
Nonspecific bacterial	4	3
Ectropion (only)	10	6
Chronic cystic cervicitis	12	4
Erosion	39	19
Total	68	32

*The same criteria for the diagnoses listed in Table II were used by all examiners. The differentiation between erosion and ectropion was in accordance with Novak's[1] definition.

Thus, the total numbers recorded in Table II exceed the numbers of patients with pathology listed in Table I. As can be seen, there were no cases of vaginitis due to trichomonal or monilial organisms in the treated group. Similarly, the incidence of ectropion, chronic cystic cervicitis, and erosion was lower in that group.

As could be expected, some of the patients had marital relations and some used douches during the six-week postpartum period, disregarding our instructions. Intercourse was reported by 25 per cent of the therapy group and by 27 per cent of the control group, approximately the same number in both groups. Douches were used by 8 per cent in the therapy group and by 17 per cent in the control group. The patients in the latter group commented that they thought douches were indicated because of a feeling of uncleanliness or because of a bad odor or a profuse discharge from the vagina.

There were two cases of questionable sensitivity to the use of the drug.

One patient was a 19-year-old, gravida ii, para ii, white woman who had reported no previous cervical or vaginal disease. She stated that after she had used the sulfisoxazole cream for three days, she noted a marked itching of the vulva and perineal skin. According to the patient there was no rash. She did not consider the condition severe enough to seek medical aid. She did stop the use of the cream, however, and the itching subsided within 24 hours.

The other was a 34-year-old, gravida vi, para iv, white woman who had a marked leukorrhea with vaginal burning and itching during her prenatal course. She reported that there was burning of the vagina upon insertion of the vaginal cream and that after using it for four days she had a generalized pruritic body rash. The patient was seen by a dermatologist 24 hours later. His impression was that the rash was an allergic response to the topical use of sulfisoxazole. She discontinued the use of the cream and recovered within 48 hours. At the time of her re-examination, no rash was apparent.

Although this series is small, nevertheless, it is our definite impression that the patients who used the sulfisoxazole cream during the postpartum period had better vaginal hygiene, well-healed episiotomies, and better epithelization of cervices than those of the control group. The vaginal mucosa of the patients in the treated group appeared cleaner and healthier than that of the untreated controls.

A majority of the patients stated that they particularly liked the cream and would want to use it again during subsequent postpartum periods. They reported a marked decrease of postpartum leukorrhea, and of odor of the lochia. These patients frequently commented that they felt "cleaner."

Summary

1. Gantrisin cream was studied in 150 cases to determine its merits in the prevention of postpartum cervicitis and vaginitis. An identical number of untreated patients served as controls.

2. Treatment which was initiated on the seventh postpartum day consisted of the administration of one applicatorful of Gantrisin cream nightly for two to three weeks. Re-examination of all 300 patients, six weeks after delivery, showed a significantly lower incidence of vaginitis, cervicitis, and erosion in the treated group.

3. The results of the study indicate that Gantrisin cream is a valuable addition to the therapeutic armamentarium for the postpartum patient.

Reference

1. Novak, Emil: Gynecologic and Obstetric Pathology, Philadelphia, 1952, W. B. Saunders Company, pp. 73-74.

THE CLINICAL EVALUATION OF 2-ACETYLAMINO-5-NITRO-THIAZOLE,* AN ORALLY EFFECTIVE TRICHOMONACIDE

ALBERT A. PLENTL, PH.D., M.D., MARY JANE GRAY, M.D., EARL D. NESLEN, M.D., AND SALIM J. DALALI, M.D., NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons and the Presbyterian Hospital, New York)

THE treatment of vaginal trichomoniasis leaves a great deal to be desired. A specific therapeutic agent which could cure this parasitic infection has not been found and none of the various types of therapy commonly used are satisfactory. The multiplicity of conflicting claims on the success of the treatment of trichomoniasis may be due to factors concerned with the diagnosis, the criteria of cure, and the difficulty of establishing a satisfactory series of controls. Further, the exhaustive monograph by Trussell[1] shows that only a fraction of the agents used were trichomonacidal in vitro. The possibility exists, therefore, that the disease may be self-limiting or that almost any supportive therapy directed to restoring the normal vaginal flora and acidity may occasionally lead to a lasting immunity.

The diagnosis is based upon the signs and symptoms of vulvovaginitis, the characteristic purulent, foamy discharge, and the demonstration of parasites in this discharge. The efficiency of three diagnostic techniques has been evaluated by Kean and Day,[2] who concluded that the culture method of Kupferberg, Johnson, and Sprince,[3] was the most reliable and gave roughly 30 per cent more positive tests than the hanging-drop method or the Papanicolaou smear. The last two methods appeared to be equally sensitive but the Papanicolaou smear required too much technical skill for routine diagnosis. To date there is no report in the literature on the clinical evaluation of trichomonacidal agents which are based upon the diagnosis by the culture method. One must conclude that the parasitologic cure rates of earlier reports were actually considerably lower than claimed.

The variation in the criteria of cure established by various investigators makes it difficult to compare their data. The presence or absence of parasites in the vaginal discharge, based upon the hanging-drop method or modifications thereof, is insufficient, partly because the test is only 70 per cent accurate and partly because the parasites may be harbored in Skene's or Bartholin's glands or the lower urinary tract. The requirement of freedom from parasites over prolonged periods, e.g., three or four months, as advocated by many clinicians, is of questionable significance unless the possibility of reinfection by the sexual partner is excluded.

*Tritheon, supplied by the Ortho Research Foundation, Raritan, N. J.

Because of the fact that so many nonspecific and inert compounds alone or in combination with jellies or douches lead to an apparent cure, a satisfactory series of controls is difficult to establish. A rigorous comparison would necessitate the study of a series of patients who have received no treatment whatsoever. An asymptomatic series of controls can easily be established, but symptomatic patients cannot be denied a minimal amount of therapy.

The local application of chemicals with or without trichomonacidal action can be expected to exert its effect only wherever it has been applied. Since foci of infection may occur in neighboring structures and glands it is unlikely that local therapy will ever have a high measure of success. The stimultaneous application of various agents to vagina, bladder, and rectum as advocated by many European clinicians could only partly overcome this obstacle.

An ideal trichomonacidal agent should exert its effect systemically which would ensure its even distribution throughout the body and thus reach all mucous membranes and infected glands. The advantages of systemic rather than local therapy need not be emphasized since the logic of this manner of treatment has been pointed out by many students of this problem. Attempts to eradicate the parasite by systemic or oral administration have been made by several investigators but their results are difficult to evaluate.

Spirocid, an oral preparation containing acetylamino-hydroxy-phenyl-arsonic acid, was claimed by Rodecurt[4] to have a remarkable effect when used in what he called "concentric therapy." This consisted of oral administration of Spirocid and local application of the same material in the form of vaginal suppositories. On 73 patients treated in this manner, Rodecurt reported a "cure rate" of 75 per cent. Pattyson,[5] on the other hand, found this compound to have no effect at all when administered by mouth and reported similar failures for Fowler's solution (arsenic), sodium arsenate, Mapharsen, carbarsone (p-carbaminophenyl-arsonic acid) and intramuscular bismuth. Salvarsan was found to be of no value in the treatment of vaginal trichomoniasis.[6]

Quinine and chloral hydrate[7] or the administration of lime[4] was thought to be an effective agent for the treatment of intestinal trichomoniasis, now known to be due to *T. hominis*[1] rather than *T. vaginalis*. Infections of the male urinary tract were eradicated in seven of eight infected cases with calcium mandelate,[8] while the systemic administration of Urotropin (hexamethylenetetramine) and sodium acid phosphate had little or no effect.[9]

None of these agents are appreciably trichomonacidal in vitro[1] and could not possibly be expected to have a primary effect on the flagellates in vivo within the anticipated concentration ranges of body fluids. A series of compounds with established protozoacidal, though not necessarily trichomonacidal, properties were tested by Schwartzwelder, Mule, Frye, and Vella.[10] No significant effect on vaginal trichomoniasis could be demonstrated. These authors could not confirm Carpenter's[11] optimistic report on systemic chloroquine therapy.

A compound with exceptional trichomonacidal properties has recently been described by Cuckler, Kupferberg, and Millman.[12] This substance, 2-acetyl-

amino-5-nitrothiazole (Tritheon) is a water-soluble, stable, crystalline organic compound. It is relatively nontoxic to experimental animals with pronounced in vivo trichomonacidal properties on experimentally infected mice and monkeys. The present communication is a report on a preliminary clinical evaluation of this drug.

Methods

Culture Technique.—The technique of obtaining cultures of the vaginal discharge was essentially that described by Kean and Day[2] using the simplified trypticase medium of Kupferberg, Johnson, and Sprince,[3] without the use of subcultures. The seeded media were incubated at 37° C. and read on the second day. If negative, the cultures were re-examined on the fifth day. The test was considered negative if no parasites were seen on the fifth day. During this study a total of 1,730 such cultures were performed on unselected gynecologic patients and pregnant women.

Hematologic Methods.—The packed red-cell volume, blood count including differential, plasma protein and urine analyses were performed in the accepted routine manner. Hemoglobin was determined by the usual colorimetric procedure.

Selection of Patients.—In order to have available for study a continuous supply of infected patients it was necessary to establish a specific screening routine for the outpatient department. The first five gynecologic patients seen by the clinic resident each day were used for this test. Regardless of the presence or absence of symptoms, cultures of the vaginal discharge from the posterior fornix were obtained before any examination was performed. If these cultures were reported as positive, the patients were asked to return in order to submit to further evaluation, provided no other urgent treatment was indicated. An attempt was then made to rule out complicating pathologic changes and to eliminate nonspecific infections of the cervix, endometrium, upper and lower urinary tract, Neisserian infections, and senile vaginitis, all of which might cloud the interpretation of the data.

The first five pregnant patients who presented themselves for an antepartum workup were screened in an analogous manner. Mild forms of clinical candidiasis were not considered a contraindication for therapy.

Incidence.—Among 818 unselected gynecologic patients the culture method showed the presence of parasites in 258, an incidence of 31.6 per cent. Seventy-five of the patients were found to be not suited for further study because of one or more of the previously mentioned complicating factors. Of the remaining 183, 106 had moderate to severe vaginitis and 77 were asymptomatic.

Among 214 routine cultures on pregnant patients, 43, or 20 per cent, were found to be positive for trichomonads. All of them complained of mild leukorrhea. Thirty of these patients were subjected to oral Tritheon therapy after a satisfactory dosage limit had been established.

Dosage Limits.—Although careful studies of chronic toxicity have been carried out on 6 species of animals,[12] the first clinical trials would require a careful study of dosage limits. The two objective reactions noted particularly in dogs and monkeys were anorexia and dark pigmentation of the urine. When 2-acetylamino-5-nitrothiazole was administered to monkeys in amounts not exceeding 20 mg. per kilogram of body weight per day over a period of eleven weeks, no objective side reactions were noted. This amount of material would correspond to about 1,000 mg. per day for an average adult human being. Based upon these considerations, the upper limit of safety was arbitrarily chosen as 600 mg. per day and preliminary trials on volunteers indicated that this amount was tolerated reasonably well.

Results

All patients were given one course of therapy which consisted of 24 gelatin capsules of 2-acetylamino-5-nitrothiazole, each containing 150 mg. to be taken four times a day. Five days after completion of therapy the patients were asked to return for clinical evaluation and another culture was taken. Since the incidence of undesirable side reactions was found to be too high, the dosage was lowered to 450 mg. per day without appreciable change.

One hundred twenty-five patients so treated showed a parasitologic cure rate of 37 per cent. Forty-four, or 35 per cent, of these patients had subjective undesirable side reactions which could be attributed to the medication. Slightly more than one-half (55 per cent) of all the patients had signs and symptoms of moderate to severe vaginal trichomoniasis. Sixty-seven per cent of these became asymptomatic after therapy and 38 per cent of these were free of parasites.

Further lowering of the daily dosage limit to 300 mg. and using enteric-coated tablets reduced the incidence of side effects to about 5 per cent without affecting the parasitologic cure rate. Forty-eight gynecologic patients who had received 300 mg. per day for seven days showed a parasitologic cure rate of 35 per cent. Thirty unselected pregnant patients were then treated in an identical manner. Ten of these patients, or 33.3 per cent, were found to be free of parasites after one such course, but denied symptomatic improvement.

Ten asymptomatic patients picked at random were followed at monthly intervals in an effort to establish a control series. Parasites were demonstrable in all ten patients after a period of three months. None of them noticed any change in the character or amount of vaginal discharge.

Hematologic studies were limited to the first 44 patients who had received the original high dosage of 600 mg. per day. There was no demonstrable change in hematocrit, red- and white-cell counts, plasma protein concentration, and routine urine analyses before and after treatment.

The subjective side reactions were disturbing to a number of patients and therapy had to be discontinued in 12 per cent of those patients who had received 450 mg. per day or more. The specific complaints in the order of frequency were nausea, abdominal cramps, anorexia, and occasionally a dark discoloration of the urine. When enteric-coated tablets in a total dosage of 300 mg. per day were given over a period of 7 to 10 days, these side reactions were minimal and none discontinued therapy because of them.

Comment

This preliminary investigation was carried out for the purpose of demonstrating that a parasitologic cure of vaginal trichomoniasis can be accomplished by the oral administration of an effective trichomonacidal agent. An objective evaluation of this trichomonacidal agent was possible only because an accurate culture method for the detection of parasites was available which can now be used as a routine procedure. Clinical improvement, though desirable, and moderate toxic side reactions, though undesirable constituted an incidental finding which should not obscure the major object of this attempt, namely, the eradication of parasites by systemic rather than local therapy.

Evidence has been presented that 2-acetylamino-5-nitrothiazole does eradicate the parasites in about 35 per cent of all patients regardless of the presence or absence of symptoms. The troublesome symptomatic side effects were decreased to negligible proportions by reducing the daily dose from 600 mg. to 300 mg. with slight prolongation of therapy.

Despite the severe conditions of this clinical experiment, a symptomatic improvement of 67 per cent of infected patients was noted, a result comparable to the "cure rate" of many clinical reports. Since a variety of inert materials, when applied locally, exert a beneficial effect,[1] a higher symptomatic cure rate could be expected by combining the oral administration of this trichomonacidal agent with nonspecific local therapy directed toward the establishment of normal vaginal flora.

Summary

Routine examination of vaginal smears by the culture method of Kupferberg, Johnson, and Sprince showed that 31.6 per cent of gynecologic clinic patients harbored *Trichomonas vaginalis*. Twenty per cent of pregnant patients were found to be infected when the same diagnostic technique was used. About 60 per cent of these patients had symptoms attributable to the disease.

A potent trichomonacidal agent, 2-acetylamino-5-nitrothiazole, was shown to be effective when administered orally. The parasites were eradicated in 35 per cent of infected patients regardless of the presence or absence of symptoms when the drug was administered in a daily dose of 300 mg. as enteric-coated tablets for a period of seven to ten days. With dosages exceeding 450 mg. per day, side reactions such as anorexia, abdominal cramps, nausea, and dark discoloration of the urine became pronounced without a corresponding rise in the parasitologic cure rate. There was no demonstrable change in the hemograms of these patients during and after therapy.

Evidence has been presented that *T. vaginalis* can be eradicated by the systemic action of a new trichomonacidal agent.

References

1. Trussell, R. E.: Springfield, Ill., 1947, Charles C Thomas.
2. Kean, B. H., and Day, E.: Am. J. Obst. & Gynec. 68: 1510, 1954.
3. Kupferberg, A. B., Johnson, G., and Sprince, H.: Proc. Soc. Exper. Biol. & Med. 67: 304, 1948.
4. Rodecurt, M.: Ztschr. Geburtsh. u. Gynäk. 112: 362, 1936.
5. Pattyson, R. A.: New York J. Med. 37: 41, 1937.
6. Ackermann, A.: Dermat. Ztschr. 71: 132, 1935.
7. Rodecurt, M.: Ztschr. Geburtsh. u. Gynäk. 107: 217, 1934.
8. Strain, R. E.: J. Urol. 54: 483, 1945.
9. Allen, E., and Baum, H. C.: Am. J. Obst. & Gynec. 45: 246, 1943.
10. Schwartzwelder, C., Mule, J. G., Frye, W. W., and Vella, F.: J. Parasitol. 40: 25, 1954 (Abst.).
11. Carpenter, E.: M. Times 80: 129, 1952.
12. Cuckler, A. C., Kupferberg, A. B., and Millman, N.: J. Parasitol. (In press.)

INFECTIONS OF THE URINARY TRACT IN OBSTETRICAL AND GYNECOLOGICAL CONDITIONS WITH SPECIAL REFERENCE TO THE USE OF COMBINED ANTIBIOTICS

J. A. McCredie Smith, M.D., M.R.C.O.G., Manchester, England, and
J. Smith, M.D., D.Sc., F.R.C.P., D.P.H., Aberdeen, Scotland

(From the Department of Obstetrics and Gynaecology, Manchester University, and the Regional Laboratory, City Hospital, Aberdeen)

WITH the introduction of first the sulfonamides and later the antibiotics, a great advance was made in the therapy of infections of the urinary tract. Recently published papers on the use of various antibiotics, however, have sometimes implied that the results obtained are not quite so satisfactory as had been originally anticipated. The limitations of the various antibiotics are now more fully understood and so also are many of the factors which may interfere with their full action in the human tissues.

Against many of the gram-negative organisms associated with infections of the urinary tract the newer antibiotics, chloramphenicol and the tetracyclines, mainly produce bacteriostasis. Streptomycin, on the other hand, is often unique in its action on coliform types in that it is frequently bacteriostatic and bactericidal in the same concentrations. Furthermore, if it is not bactericidal, then, unfortunately, surviving organisms may rapidly acquire a high degree of resistance to it. It may be that, in vivo, the bactericidal activity of antibiotics is equal to, or even more important than, their bacteriostatic action, particularly in situations such as in a hollow viscus. The combination of two antibiotics so as to produce an additive or even synergistic effect might lessen the possibility of the appearance of resistant variants. Apart from the complete elimination of the infecting organism, it might be possible to utilize the bactericidal powers of streptomycin by combining with it some other antibiotic and thus lessen the chance of the emergence of a resistant strain. To chloramphenicol and the tetracyclines resistance is not so easily acquired by the Gram-negative infecting agents of the urinary tract, though with staphylococci this is another matter. Miller and associates[5] reported that oxytetracycline combined with streptomycin in the treatment of pulmonary tuberculosis seems to inhibit the development of resistance to tubercle bacilli. When, however, more than one type of organism is associated with the infection then combined therapy would also appear to be entirely logical. It was to investigate these possibilities that this research was undertaken.

Bacteriological Investigation

The methods used for the examination of specimens of urine have already been described (Smith and Smith[6]) and so also have those used in testing for

sensitivity. The paper discs impregnated with antibiotics are again applied to all primary routine plate cultures, but for the detailed examination of the sensitivity of cultures the effects of graded amounts of antibiotic in nutrient broth were studied for their bacteriostatic, and, perhaps, of more importance, for their bactericidal action.

1. Sensitivity Test on Bact. coli.—

In a previous paper it was shown that oxytetracycline (Terramycin) had a markedly bacteriostatic but little bactericidal action on all strains tested, and that streptomycin was bacteriostatic and bactericidal—the bacteriostatic effect being practically equivalent to the bactericidal action. Furthermore it was found that certain strains of *Bact. coli,* when passaged in broth cultures containing increasing amounts of these antibiotics, developed resistance only slowly to oxytetracycline but often rapidly and markedly to streptomycin. When the same strains of *Bact. coli* were passaged in broth cultures containing combined oxytetracycline and streptomycin, the development of resistance was inhibited to a very considerable extent.

In the present investigation the sensitivity of 10 new strains of *Bact. coli* to chloramphenicol (C), oxytetracycline (O), and streptomycin (S) was first tested and then their sensitivity to combinations of all three (C + O, C + S, O + S). The results of these tests are given in Table I, where it is seen that C, O, and the combinations C + O, C + S, and O + S, are equally bacteriostatic, and definitely more so than S. When, however, the bactericidal action was examined O was not bactericidal even at 100 μg per milliliter, C and C + O had almost equal bactericidal powers at 100 and 50 μg per milliliter, S and C + S were more effective, while O + S was slightly more bactericidal than C + S.

TABLE I. SENSITIVITY OF 10 STRAINS OF BACT. COLI TO ANTIBIOTICS

	NO. OF STRAINS SHOWING BACTERIOSTASIS AFTER 24 HOURS AT 37° C. IN BROTH CONTAINING: (μG. PER ML.)							NO. OF STRAINS SHOWING EVIDENCE OF BACTERICIDAL ACTION AFTER 24 HOURS AT 37° C. IN BROTH CONTAINING: (μG. PER ML.)						
ANTIBIOTIC*	100	50	25	12.5	6.25	3.1	1.5	100	50	25	12.5	6.25	3.1	1.5
C	10	10	10	10	10	8	2	6	5	2	1	0	0	0
O	10	10	10	10	10	6	2	0	0	0	0	0	0	0
S	8	7	6	5	5	3	2	8	7	6	5	3	2	1
C + O	10	10	10	10	8	6	4	6	4	2	0	0	0	0
C + S	10	10	10	10	10	8	3	8	8	5	2	0	0	0
O + S	10	10	10	10	10	9	3	10	9	6	4	2	0	0

*C = chloramphenicol.
O = oxytetracycline.
S = streptomycin.

The results of passaging the 10 strains in nutrient broth containing increasing concentrations of C, O, S, C + O, C + S, and O + S and then retesting their sensitivity to C, S, and O are given in Tables II, III, and IV. When retested against chloramphenicol (Table II) the only essential difference from the results obtained in the control series (Table I) was that in the bactericidal tests after passage in chloramphenicol a certain degree of resistance had been developed against this antibiotic but not against the others. Furthermore, even in the tests following passage in combined antibiotics this resistance was notable especially after passaging in C + O. When the passaged strains were retested against streptomycin (Table III) the resistance developed after passage in S alone was very high and the resistance was also increased following the use of C + S but they showed little change after treatment with S + O. Thus, after treatment in S, 8 strains became insensitive to 1,000 μg of

streptomycin and 2 to 200 μg. After treatment in C + S, 4 strains had become insensitive to 1,000 μg of S per milliliter and 2 to 200 μg per milliliter. When the passaged strains were retested against O there was no essential difference between these results and those obtained in the control tests.

TABLE II. SENSITIVITY OF 10 STRAINS OF BACT. COLI TO ANTIBIOTICS AFTER 10 PASSAGES IN NUTRIENT BROTH CONTAINING CHLORAMPHENICOL

	NO. OF STRAINS SHOWING BACTERIOSTASIS AFTER 24 HOURS AT 37° C. IN BROTH CONTAINING: (μG. PER ML.)							NO. OF STRAINS SHOWING EVIDENCE OF BACTERICIDAL ACTION AFTER 24 HOURS AT 37° C. IN BROTH CONTAINING: (μG. PER ML.)						
ANTIBIOTIC	100	50	25	12.5	6.25	3.1	1.5	100	50	25	12.5	6.25	3.1	1.5
C	10	9	5	0	0	0	0	4	2	0	0	0	0	0
O	10	10	10	10	10	5	1	0	0	0	0	0	0	0
S	9	9	8	7	5	4	1	8	7	6	3	2	1	0
C + O	10	10	10	10	6	2	0	3	1	0	0	0	0	0
C + S	10	10	10	6	4	0	0	7	5	1	0	0	0	0
O + S	10	10	10	10	10	8	3	10	6	4	3	1	0	0

TABLE III. SENSITIVITY OF 10 STRAINS OF BACT. COLI TO ANTIBIOTICS AFTER 10 PASSAGES IN NUTRIENT BROTH CONTAINING STREPTOMYCIN

	NO. OF STRAINS SHOWING BACTERIOSTASIS AFTER 24 HOURS AT 37° C. IN BROTH CONTAINING: (μG. PER ML.)							NO. OF STRAINS SHOWING EVIDENCE OF BACTERICIDAL ACTION AFTER 24 HOURS AT 37° C. IN BROTH CONTAINING: (μG. PER ML.)						
ANTIBIOTIC	100	50	25	12.5	6.25	3.1	1.5	100	50	25	12.5	6.25	3.1	1.5
C	10	10	10	10	8	4	2	5	5	1	1	0	0	0
O	10	10	10	10	10	5	2	0	0	0	0	0	0	0
S*	0	0	0	0	0	0	0	0	0	0	0	0	0	0
C + O	10	10	10	10	5	1	0	4	1	1	0	0	0	0
C + S†	4	2	0	0	0	0	0	4	2	0	0	0	0	0
O + S	10	10	6	2	0	0	0	10	10	5	2	0	0	0

*8 strains insensitive to 1,000 μg streptomycin.
2 strains insensitive to 200 μg streptomycin.
†4 strains insensitive to 1,000 μg streptomycin.
2 strains insensitive to 200 μg streptomycin.

TABLE IV. SENSITIVITY OF 10 STRAINS OF BACT. COLI TO ANTIBIOTICS AFTER 10 PASSAGES IN NUTRIENT BROTH CONTAINING OXYTETRACYCLINE

	NO. OF STRAINS SHOWING BACTERIOSTASIS AFTER 24 HOURS AT 37° C. IN BROTH CONTAINING: (μG. PER ML.)							NO. OF STRAINS SHOWING EVIDENCE OF BACTERICIDAL ACTION AFTER 24 HOURS AT 37° C. IN BROTH CONTAINING: (μG. PER ML.)						
PASSAGED IN ANTIBIOTIC	100	50	25	12.5	6.25	3.1	1.5	100	50	25	12.5	6.25	3.1	1.5
C	10	10	10	8	8	8	1	0	0	0	0	0	0	0
S	10	10	10	8	8	8	3	0	0	0	0	0	0	0
O	10	10	10	6	2	2	0	0	0	0	0	0	0	0
C + O	10	10	10	8	2	0	0	0	0	0	0	0	0	0
C + S	10	10	10	10	4	2	0	0	0	0	0	0	0	0
O + S	10	10	10	8	8	6	0	0	0	0	0	0	0	0

2. Effect of Antibiotics on Strains of B. proteus.—

Urinary tract infections with *B. proteus* are often difficult to treat and after treatment the infections often recur. A number of strains of this organism were collected and tested against the antibiotics in the same way as the *Bact. coli* strains had been examined. The results are given in Table V,

from which it is seen that streptomycin (S) was the most active antibiotic from the point of view of both bacteriostasis and its bactericidal action, chloramphenicol (C) was more bacteriostatic than chlortetracycline (Aureomycin, A) and oxytetracycline (O) but all 3 antibiotics failed to show any bactericidal action even at 100 μg per ml. Furthermore, when the strains were tested against paired antibiotics, only the pairs containing streptomycin really produced effective bacteriostatic and bactericidal actions and these were only slightly more marked than those obtained with streptomycin alone. No tests were carried out to see if the development of resistance to streptomycin could be inhibited when passaged in broth containing combined antibiotics.

TABLE V. SENSITIVITY OF 15 STRAINS OF B. PROTEUS TO ANTIBIOTICS

	NO. OF STRAINS SHOWING BACTERIOSTASIS AFTER 24 HOURS AT 37° C. IN BROTH CONTAINING: (μG. PER ML.)							NO. OF STRAINS SHOWING EVIDENCE OF BACTERICIDAL ACTION AFTER 24 HOURS AT 37° C. IN BROTH CONTAINING: (μG. PER ML.)						
ANTIBIOTIC*	100	50	25	12.5	6.25	3.1	1.5	100	50	25	12.5	6.25	3.1	1.5
A	7	4	4	3	0	0	0	0	0	0	0	0	0	0
C	13	12	9	2	0	0	0	0	0	0	0	0	0	0
S	15	15	14	14	10	0	0	15	15	14	5	0	0	0
O	6	5	4	4	4	0	0	0	0	0	0	0	0	0
A + S	15	15	15	14	6	1	0	15	15	12	7	0	0	0
C + S	15	15	15	15	14	13	0	15	15	11	6	1	0	0
O + S	15	15	15	15	14	0	0	15	15	15	15	3	0	0
A + C	15	11	3	3	2	0	0	0	0	0	0	0	0	0
A + O	4	3	2	2	1	0	0	0	0	0	0	0	0	0
C + O	15	13	9	5	4	0	0	0	0	0	0	0	0	0

*A = Aureomycin (chlortetracyline).

Treatment of Bact. coli Urinary Tract Infections.—

In the first series[6] the cases were divided into two groups, one being treated with oxytetracycline alone and the second with combined streptomycin and oxytetracycline. The results showed that, though oxytetracycline was a satisfactory therapeutic agent, the combination of streptomycin and oxytetracycline was even more effective and produced more rapid subsidence of symptoms. Furthermore, with the short three-day course of combined antibiotics the side effects were practically negligible.

In the continuance of the investigation further cases have now been treated with combined streptomycin and oxytetracycline, and combined streptomycin and chloramphenicol. At first it was hoped to have two balanced series of cases treated with chloramphenicol, and combined streptomycin and chloramphenicol, but the results following the use of chloramphenicol alone were occasionally disappointing and the cases were then treated with the combined antibiotics only. In all, 95 cases have now been observed during the investigation (Table VI).

The course of treatment of each series of cases was as follows:

A. Oxytetracycline series; oral oxytetracycline, 0.5 Gm. every six hours for 72 hours followed by 0.25 Gm. every six hours for a further period of 72 hours.

B. Oxytetracycline and streptomycin series; oral oxytetracycline, 0.5 Gm. every 6 hours for 3 days, and 1 Gm. of streptomycin twice daily parenterally for the same period.

C. Chloramphenicol and streptomycin series; oral chloramphenicol, 0.5 Gm. every 6 hours for 3 days, and 1 Gm. of streptomycin twice daily for the same period.

During all treatments the urine was as far as possible maintained in an alkaline condition, and 48 hours after treatment was ended further catheter specimens were obtained for bacteriological examination. It should be noted that many of the patients had been infected during or after operative procedures and therefore had not reached a state of chronicity before therapy was started. All patients were asked on discharge from the hospital to report for further examination in the outpatient department.

TABLE VI. CLASSIFICATION OF 95 CASES INFECTED WITH BACT. COLI ONLY AND TREATED WITH ANTIBIOTICS

	NUMBER TREATED WITH		
	O	O + S	C + S
Obstetrical.—			
Antepartum	3	3	8
Postpartum		2	
Gynecological.—			
Preoperative:			
Prolapse and diabetes	1		
Prolapse		1	3
Stress incontinence	2	1	3
Endometriosis		1	
Fibroids			1
Leukoplakia			1
Postoperative:			
Prolapse, repair	10	14	12
Prolapse, vaginal hysterectomy	2	3	
Stress incontinence, repair	1		2
Fibroids, hysterectomy	3		1
Endometriosis, ovariotomy	1	2	
Pyosalpinx, salpingectomy	1		
Carcinoma of cervix, radium and Wertheim hysterectomy	1		
Cervicitis, amputation		1	
Menorrhagia, dilatation and curettage		1	2
Postmenopausal hemorrhage, dilatation and curettage		1	1
Ovariotomy			1
Menorrhagia, hysterectomy			3
Vesicovaginal fistula		1	
Nongynecological.—			
Diabetes		1	
Total	25	32	38

In the group of 25 patients treated with oxytetracycline there was a satisfactory response to treatment, and failure was encountered on only one occasion. In this series 3 patients had been previously treated with sulfonamides. Combined streptomycin and oxytetracycline were used in 32 cases and all responded promptly, despite the fact that 5 had had one and 1 two courses of sulfonamides, 1 had had one course of streptomycin and two courses of chloramphenicol, 1 had had one course of sulfonamides followed by one of streptomycin, and another had one course of combined streptomycin and chloramphenicol. In the series of 38 patients treated with combined streptomycin and chloramphenicol the response was also satisfactory, and only one failed to respond. In this group 3 had failed to respond to a course of sulfonamides and 1 had failed to respond to sulfonamides and streptomycin, while the patient who failed to respond to the combined streptomycin and chloramphenicol responded to streptomycin and oxytetracycline. Most of the patients were seen again in the outpatient department of the hospital, usually about two months after discharge. In those infected with *Bact. coli*, 21 out of 25 patients treated with oxytetracycline, 27 out of 32 treated with strepto-

mycin and oxytetracycline, and 34 out of 38 treated with streptomycin and oxytetracycline reported for re-examination and all were found to be in a satisfactory condition and apparently free from urinary tract infections.

Infections Due to Various Bacteria.—

Cases of infection with bacteria other than *Bact. coli* have been encountered but the numbers of each particular type were small. Organisms belonging to the *Proteus* and *Ps. pyocyanea* groups are relatively insensitive to antibiotics in vitro and in vivo and urinary tract infections with these often defy all modern remedies, particularly when pathological abnormalities are present. Three patients infected with *B. proteus* were treated with oxytetracycline and one responded; one then received combined oxytetracycline and streptomycin and responded; the third was treated with streptomycin and chloramphenicol, but had to have a course of streptomycin and oxytetracycline before cure was effected. There were 2 cases in which *Ps. pyocyanea* was the sole causative organism, but there were 2 more cases in which *Ps. pyocyanea* was associated with *Bact. coli* and *Str. faecalis,* respectively. The first 2 were treated with streptomycin and chloramphenicol without success but responded to streptomycin and oxytetracycline. In the third case one course of streptomycin and chloramphenicol effected a cure but the same therapy only eliminated *Str. faecalis* in the fourth, though a further course of streptomycin and oxytetracycline was successful. There were 6 patients infected with *Staphylococcus pyogenes;* one failed to respond to penicillin, sulfonamides, streptomycin, oxytetracycline, and combined streptomycin and oxytetracycline. One responded to penicillin, one to oxytetracycline, and 3 to combined streptomycin and oxytetracycline. Finally, one infection with *Str. haemolyticus* responded to streptomycin and oxytetracycline, and two patients infected with Enterococci and paracolon organisms, respectively, responded to the first course of streptomycin and chloramphenicol. Re-examination of all but two of these patients at the outpatient department showed that two who had been previously infected with *Ps. pyocyanea* were now infected with B. coli. All the others were free from infection.

Comment

The in vitro sensitivity tests carried out on strains of *Bact. coli* have shown that a combination of oxytetracycline and streptomycin is a much more effective bacteriostatic and bactericidal agent than chloramphenicol or oxytetracycline alone, or combined oxytetracycline and chloramphenicol. It is also more effective bactericidally than streptomycin alone or combined streptomycin and chloramphenicol.

It is believed that the tests for bactericidal action give a better evaluation of the suitability of an antibiotic for therapeutic purposes than do tests for bacteriostasis. Furthermore, the bactericidal test which has been used has not taken into account the possible reduction of the bacterial population, but has been based on the complete destruction of all living organisms in the broth culture tubes with the specific amount of single or combined antibiotic after a contact period of 24 hours at 37° C. Tunevall and Ericsson[9] have shown that there is a considerable inactivation of chloramphenicol and the tetracyclines when dissolved in nutrient broth and held at 37° C. They estimate that in concentrations of 100 μg per milliliter, 58 per cent of oxytetracycline, 52 per cent of chloramphenicol, and only 36 per cent of chlorotetracycline remain active after 9 hours. In the tube method of testing for

bactericidal action, the full or approximately the full concentration of active antibiotic is probably maintained for a sufficient length of time to produce the necessary action on the bacterial cells and to allow a fairly accurate interpretation of the effect to be obtained.

A short course of treatment with an antibiotic might not be sufficient to produce a marked increase in resistance of surviving *Bact. coli* organisms but a longer period of treatment does tend to do so, particularly with streptomycin. The in vitro passage tests have shown that resistance to streptomycin could be developed rapidly, that resistance to chloramphenicol increased to a definite though less marked extent than with streptomycin, and that resistance to oxytetracycline developed very slowly. When, however, oxytetracycline was combined with streptomycin, the increase in resistance to streptomycin was very small, whereas in the series of tests in which chloramphenicol was combined with streptomycin, resistance developed almost as rapidly as when the organisms were passaged against streptomycin and chloramphenicol alone.

In vitro tests have also shown that streptomycin was the most effective single antibiotic against *Proteus* strains. In the combination of streptomycin with another antibiotic there was only a slightly enhanced bacteriostatic and bactericidal effect. On the other hand the combinations of chlortetracycline and chloramphenicol, chlortetracycline and oxytetracycline, and chloramphenicol and oxytetracycline produced no effective bactericidal action at 100 μg per milliliter. In this connection Armstrong and Larner[1] examined the sensitivity of 7 strains of *Ps. pyocyanea* and 4 of *P. vulgaris* to various antibiotics. In vitro tests and in vivo experimental infections in mice showed that streptomycin was the most effective drug when given alone but the combination of oxytetracycline and streptomycin gave much better results.

As regards the clinical use of antibiotics the general aspects have been recently fully reviewed by Finland,[3] the value of combined therapy has been discussed by Garrod,[4] and the therapeutics of urinary tract infections have been dealt with by Valentine and Shooter.[10] The majority of urinary tract infections are caused by gram-negative bacilli of various types, and most of these organisms are less sensitive to the antibiotics in present use than the majority of gram-positive cocci. The consensus at the moment is that in any particular infection where the causative organism is fully sensitive to a particular antibiotic, that antibiotic should be used for treatment. If, however, a combination of antibiotics produces a higher percentage of successful recoveries and, perhaps more important, fewer surviving resistant strains, then combined antibiotic therapy seems to be fully justified. In the treatment of refractory urinary tract infections Eisenberg and associates[2] have suggested the use of a triple combination of Aureomycin, oxytetracycline, and chloramphenicol.

In the course of the present investigation, infections of the urinary tract with *Bact. coli* and other gram-negative organisms have been treated with chloramphenicol, oxytetracycline, combined streptomycin and chloramphenicol, and combined streptomycin and oxytetracycline. On the basis of the

clinical results, therapy with combined streptomycin and oxytetracycline is the most effective. The response in the fairly acute case is more immediate than with other forms of medication, and in addition pain, discomfort, frequency, and fever subside more rapidly, with the urine becoming sterile in a greater percentage of cases. Furthermore, the period of therapy with the combined antibiotics is only three days as compared with a six-day course for a single antibiotic. One disadvantage in connection with the use of streptomycin is the necessity of giving it parenterally, whereas chloramphenicol and oxytetracycline are given orally. The twice daily injection of 1 Gm. of streptomycin certainly causes some inconvenience to the patient and nursing staff but this is compensated for by the shorter course of treatment. In the small series of cases in which the causative organisms were *B. Proteus* strains and *Ps. pyocyanea,* combined streptomycin and oxytetracycline seemed to be more effective than any other form of antibiotic therapy.

The treatment of cases of bacteremia due to *Bact. coli, P. vulgaris,* and *Ps. pyocyanea* in human beings with various antibiotics would seem to give a more definite answer to the effectiveness of this form of therapy. Spittel and coworkers[7, 8] at the Mayo Clinic have published two papers on the therapy of such cases. They treated 65 cases of bacteremia due to *Bact. coli* with various sulfonamides and antibiotics and the best results were obtained when dihydrostreptomycin was used in conjunction with a tetracycline. In about 60 per cent of the cases the genitourinary tract was the portal of entry, and by this form of combined therapy the death rate was reduced to 10 per cent. The same authors also found that combined dihydrostreptomycin and oxytetracycline therapy was extremely successful in 7 cases of bacteremia due to *P. vulgaris.*

Summary

1. A series of in vitro bacteriostatic and bactericidal sensitivity tests have been carried out on 10 strains of *Bact. coli* using chloramphenicol, oxytetracycline, and streptomycin, and paired combinations of all three antibiotics.

2. These tests have shown that, although the single and combined antibiotics exerted marked bacteriostatic effects, the combinations containing streptomycin produced better bactericidal actions.

3. Passage experiments, using one antibiotic at a time in vitro, showed that varying degrees of resistance, markedly to streptomycin, less to chloramphenicol, and still less to oxytetracycline, could be developed. When paired combinations of antibiotics were used in the tests, least resistance developed when the various strains were passaged in streptomycin and oxytetracycline.

4. A series of in vitro bacteriostatic and bactericidal sensitivity tests on 15 strains of *B. proteus* have shown that though chlortetracycline, chloramphenicol, and oxytetracycline had quite considerable bacteriostatic powers, they had little or no bactericidal action even in concentrations of 100 μg per milliliter. Streptomycin was more effective bactericidally but the combination of this antibiotic with one of the other antibiotics produced only a slightly more effective action.

5. A series of 111 cases of urinary tract infections associated with obstetrical and gynecological conditions have been treated with oxytetracycline, combined oxytetracycline and streptomycin, and combined chloramphenicol and streptomycin.

6. In 95 cases of *Bact. coli* infection, all three forms of medication were effective, but the combination of streptomycin and oxytetracycline seemed to produce more rapid improvement and in certain cases in which oxytetracycline or combined streptomycin and chloramphenicol had failed combined streptomycin and oxytetracycline effected a cure.

7. In a small series of infections with *B. proteus* and *Ps. pyocyanea,* treatment with combined streptomycin and oxytetracycline gave more satisfactory results than any other form of antibiotic therapy.

Thanks are due to Professor W. I. C. Morris for permission to treat patients in his Obstetrical and Gynaecological Units and for his encouragement.

References

1. Armstrong, C. W. J., and Larner, A. E.: J. Lab. & Clin. Med. **37**: 584, 1951.
2. Eisenberg, G. M., Alexander, J. D., and Fulton, H. F.: J. A. M. A. **152**: 1302, 1953.
3. Finland, M.: Brit. M. J. **2**: 1115, 1953.
4. Garrod, L. P.: Brit. M. J. **1**: 954, 1953.
5. Miller, F. L., Sands, J. H., Walker, R., Dye, W. E., and Tenpel, C. W.: Am. Rev. Tuberc. **66**: 534, 1952.
6. Smith, J. A. McC., and Smith, J.: J. Obst. & Gynaec. Brit. Emp. **49**: 145, 1954.
7. Spittel, J. A., Martin, W. J., Wellman, W. E., and Geraci, J. E.: Proc. Staff Meet. Mayo Clin. **29**: 447, 1954.
8. Spittel, J. A., Martin, W. J., Geraci, J. E., and Nichols, D. R.: Proc. Staff Meet. Mayo Clin. **29**: 225, 1954.
9. Tunevall, G., and Ericsson, H.: Antibiotics and Chemotherapy **4**: 886, 1954.
10. Valentine, F. G. O., and Shooter, R. A.: Recent Advances in Chemotherapy, London, 1953, J. & A. Churchill, Ltd., vol. 3, p. 226.

PREOPERATIVE AND OPERATIVE BLOOD VOLUME STATUS IN GYNECOLOGICAL SURGERY*

MYRON I. BUCHMAN, M.D., NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology of the Cornell University Medical College and The Woman's Clinic of the New York Hospital)

WHAT is the blood volume status of the gynecological patient entering the hospital today? Are we making too many assumptions when we say she is ready for major surgery? Most gynecologists express little concern over the routine candidate for hysterectomy or vaginal repair. Oftentimes, unless there is some extraordinary good reason to transfuse a patient preoperatively or even operatively, transfusion is not given. Soutter[1] states that even for major procedures such as hysterectomy many physicians contend that a normal hemoglobin is not necessary. He, however, applies a general rule that 12.5 Gm. of hemoglobin is a minimum prior to major surgery. There are no doubt many other similar rules of thumb, and though these are by and large satisfactory, how close to improper management do we come? Furthermore, since blood usually comes in 500 c.c. units, we tend to defer any elective transfusion until we discern a loss of at least that amount. Are we exercising good judgment?

Ideally, if we are to obtain a solution to this problem, we should follow every patient with carefully performed blood volume determinations and perhaps correct deficits as they are found. Whether blood volume determinations are done by the Evans blue,[2] iodinated albumin,[3] or tagged erythrocyte[4] methods, they involve a great deal of work and preparation and necessitate an extremely meticulous technique. These determinations are not very practical as routine procedures, and as such are not widely accepted. In addition, they are expensive and sometimes annoying to the patients. The literature indicates that not much study has been done on this subject of measured blood volumes in the field of gynecology. Therefore, in view of the lack of information, a study was undertaken to assess more adequately the blood volume picture of an unselected group of patients who came into the hospital for gynecological surgery. The surgery was performed by the resident staff. The blood volume behavior of these patients was also followed after surgery. This project seemed relatively simple at first glance, but it soon became apparent that, since there were so many sources of error, these had to be either eradicated or minimized before the study was begun.

Material and Methods

The Evans blue or T-1824 method was chosen. The newer methods utilizing tagged erythrocytes[4] are presumably more accurate for the total red blood

*Presented at the American College of Surgeons Forum, Atlantic City, New Jersey, Nov. 16, 1954.

cell mass, but consistent and satisfactory results were obtained with T-1824, and for the purposes of this investigation Evans blue was most acceptable. Gregerson[2] reported accuracy within 3 to 4 per cent in 1944, and we could duplicate his limit of error by rigidly adhering to his criteria. In fact, his criteria were enlarged by us to the extent that all of the determinations from start to finish were carried out by one person. It was only after several months of trial by various methods in the hands of one person that the results were consistent within 3 per cent. This arbitrary limit of error was checked during the study. Furthermore, if any of the rigid criteria were violated, the sample was discarded. A group of unselected patients was obtained finally and gave a reliable picture of the blood volume changes that occurred before and after operation. Consecutive cases could not be taken since small violations in technique would disqualify a patient. If the rigid criteria had been stretched occasionally, the group could have been enlarged considerably, but to do this would have meant introducing possible sources of error.

The technique finally decided upon is a modification of the Gregerson[2] method and that employed by the division of experimental surgery of the New York Hospital. Depending upon the weight of the patient, between 3.5 and 4.5 Gm. of a 0.45 per cent solution of Evans blue is weighed out in the syringe along with the needle and casing to 0.1 mg. Venepuncture is made with the needle, and another syringe is used to withdraw a pre-dye sample. No tourniquet is used. The dye is injected, and one minute allowed to elapse. The needle is withdrawn and the blood cleaned off. The determination is void if any extravasation is evident, or excessive pain is felt. Then a 10 minute sample is taken, also without the aid of a tourniquet. The blood is placed directly into heparinized hematocrit tubes at the time of withdrawal and the tubes are centrifuged for thirty minutes at 4,000 r.p.m. The empty syringe, needle, and casing are reweighed. The standard is diluted 1 to 500 and comparisons are done on a Coleman spectrophotometer-junior model at 620 mμ. The patient is always kept at basal conditions and 4 hours are permitted to elapse after meals before the procedure is undertaken. Other details, of course, are observed throughout, such as utilization of the same lot of Evans blue for all the work on the same patient, and the careful selection of veins to exclude those with any evidence of thrombosis.

Operative blood loss was measured by the gravimetric technique. This technique[5-6] does not recover all of the blood lost to the circulation, but is reasonably accurate. Postoperative blood volumes were done on the third postoperative day routinely, and in addition at times on the first or second postoperative day. Usually, the blood volume determination showed a greater blood loss than the gravimetric technique could account for, but I think the gravimetric technique gives a more reliable picture of operative blood loss, since the third-day blood volume may include postoperative oozing in addition to that lost at the time of operation.

Definitions of Terms

Before consideration of results is undertaken, it must be understood that the clinically determined T-1824 blood volumes in preoperative patients rarely equal the ideal values. For ideal values we use Randall's[7] figures based on several thousand determinations (45 c.c. per kilogram for plasma volume, 32 c.c. per kilogram for red blood cell mass in women under 50 years, 28.6 c.c. per kilogram for women over 50). The determined blood volume is below normal in most cases. This diminished volume is reduced further by the blood

loss at operation. The two combined (preoperative blood volume deficit and operative blood loss) are called final deficit in blood volume below the ideal value.

Final deficit = preoperative blood volume deficit + operative blood loss – replacement transfusions

For the moment, let us assume that transfusions are not available. Deficits then would be even greater, and these deficits are potentially present. Accordingly, the term potential deficit is used to denote the original blood volume deficit plus operative blood loss without replacement transfusion.

Potential deficit = preoperative blood volume deficit + operative blood loss

Potential deficit gives us an idea of how much of a reduction in blood volume a patient may have to tolerate, whereas final deficit shows us how much a patient did tolerate.

In addition to regarding the ideal values as an index of reference, the clinically determined T-1824 blood volumes were chosen as a base line. Operative blood loss in excess of or exclusive of replacement transfusion reduced the T-1824 blood volumes as the patient entered the postoperative period. For the purpose of analysis, we have utilized the terms potential and final deficits of known volumes to designate the percentage deficit the operation made in the T-1824 volumes of these patients.

Results

For evaluation of the results the patients were divided into two groups. The first group consisted of 20 patients who entered the hospital for abdominal hysterectomy and possibly oophorectomy. Nineteen had pelvic disease in the form of a tumor, which was generally responsible for pain or bleeding, and one had pelvic tuberculosis. Contrasted to this, the second group consisted of 20 patients who entered the hospital for vaginal plastic procedures (alone or accompanied by vaginal hysterectomy or amputation of the cervix). The patients in the latter group were generally older, had borne more children, and were beginning to suffer from chronic or degenerating diseases such as hypertension and arteriosclerosis. If strength and resilience of tissues are indices of health, these patients would be below normal.

TABLE I. PREOPERATIVE T-1824 DETERMINED BLOOD VOLUME VALUES EXPRESSED IN PERCENTAGE OF IDEAL VALUES

	AVERAGE (%)	MAXIMUM (%)	MINIMUM (%)
Abdominal.—			
Blood volume	-16.4	+4.5	-34.6
Plasma volume	-8.5	+19.3	-31.3
RBC mass	-26.7	-2.5	-51.0
Vaginal Repair.—			
Blood volume	-15.8	+3.6	-33.2
Plasma volume	-13.2	+15.7	-29.2
RBC mass	-19.6	+6.3	-42.0

The blood volume picture of all patients considered in this study upon entering the hospital is summarized in Table I, and since we call Randall's figures ideal values, the results are expressed in per cent of ideal values. It was not surprising to find that the preoperative blood volumes in both groups were below normal. Other studies[8] substantiated this finding; in fact, in an unpublished report on a group of surgical patients at Presbyterian Hospital, Columbia University, College of Physicians and Surgeons, 65 per cent required one or more transfusions to restore their blood volume to normal.

The average blood volume deficit in the vaginal group was –15.8 per cent and in the abdominal group –16.4 per cent. Figs. 1 and 2 on which preoperative blood volumes and their respective components, red blood cell mass and plasma volume, are plotted one above the other in order of decreasing blood volumes demonstrate that the blood volume distribution from maximum to minimum of the two groups is essentially the same. Even if we were to go so far as to consider a possible source of error of 10 per cent, which is a liberal admission, almost half of the patients would require transfusion before operation to bring them to normal.

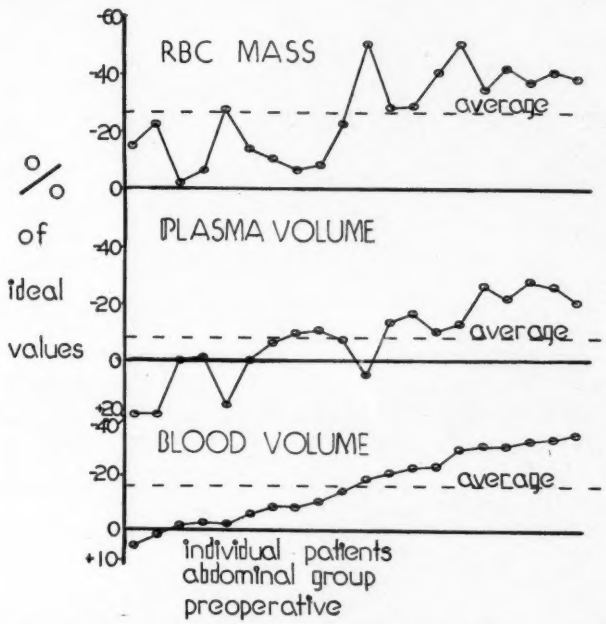


Fig. 1.—Preoperative values of abdominal hysterectomy patients expressed in per cent of ideal values. The lowest level contains the preoperative blood volumes of 20 patients expressed in per cent of ideal values. The blood volumes are plotted in order of decreasing magnitude. The respective components of each blood volume, the plasma volume and red blood cell mass, are plotted directly above one another over each blood volume point.

In order to understand more fully the significance of the results shown in Figs. 1 and 2, our attention should be turned to the components of the blood, the red blood cell mass and the plasma volume. Both of these components can vary independently of each other. Examination again of Table I and Figs. 1 and 2 shows that there is a difference in the deficits of the red blood cell mass. The average deficit in the vaginal group was –19.6 per cent and in the abdominal group the deficit was –26.7 per cent. The distribution of the red blood cell mass deficit was such that the larger blood volume deficits in the abdominal group were due to a depletion primarily in the red blood cell mass, whereas in the vaginal group larger blood volume deficits were due to a deficiency in both plasma volume and red blood cell mass. This is especially interesting since 14 patients in the abdominal group complained of bleeding and 10 of them had red blood mass deficits varying from 28 to 51 per cent below the ideal values. The only other patient who had severe depletion was one who suffered from pelvic tuberculosis. The history of bleeding was the only significant clue to a lowered red blood cell mass in most instances. On the other hand, even though 4 patients bled excessively, they were able to restore their red blood cell mass to reasonably normal limits.

In the abdominal group in which moderately severe deficits in the red blood cell mass were registered, some attempt was made to restore the blood volume to ideal by enlarging the plasma compartment. This attempt was far from satisfactory, however, and the plasma volume was replaced only partially. It appears more advantageous for the blood volume to contract rather than for the red blood cells to be diluted too greatly by an overcompensated plasma volume. Partial compensation was probably responsible for the plasma volume in the hysterectomy group being only –8.5 per cent of ideal whereas in the vaginal group it was –13.2 per cent of ideal.

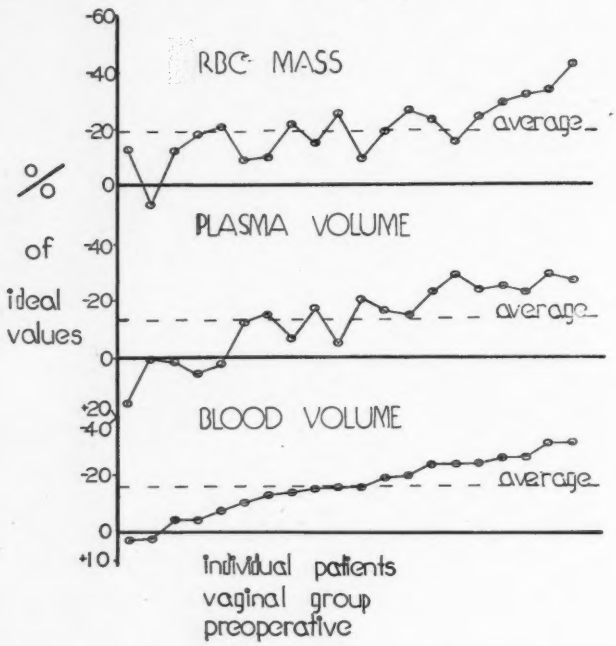


Fig. 2.—Preoperative values of vaginal plastic patients expressed in per cent of ideal values. For explanation refer to Fig. 1.

It seems apparent from the foregoing that the patient entering the hospital for operation usually harbors a blood volume below ideal values. This already diminished blood volume will then be further reduced by the blood loss at operation. How much below an ideal blood volume value can a patient potentially go without transfusion, and at what levels do we generally transfuse patients? Last, what is the final state of the blood volume picture?

First let us consider the potential loss (preoperative blood volume deficit plus operative blood loss exclusive of transfusion). We find that in the abdominal group (Table II and Fig. 3) the average potential deficit in blood volume was as great as –24.7 per cent and in the vaginal group (Fig. 4) –28.3 per cent with maximums, respectively, of –45.6 per cent and –54 per cent. The distribution from maximum to minimum was essentially the same in both groups. If the loss in blood volume had been rapid, 50 per cent of the patients would have gone into shock. However, the deficit is a combination of chronic depletion and rapid loss (operative blood loss) and does not affect the vascular apparatus as would rapid loss alone. Nevertheless, it is surprising to find that the procedures in both groups, which most of us today regard as innocuous, can terminate with a deficit in blood volume which at times may be as high as 45 to 50 per cent of the ideal volume.

TABLE II. POTENTIAL LOSS IN BLOOD VOLUME EXPRESSED IN PERCENTAGE OF IDEAL VALUES

	AVERAGE (%)	MAXIMUM (%)	MINIMUM (%)
Abdominal	-24.7	-45.6	-9.1
Vaginal	-28.3	-54.0	-9.8

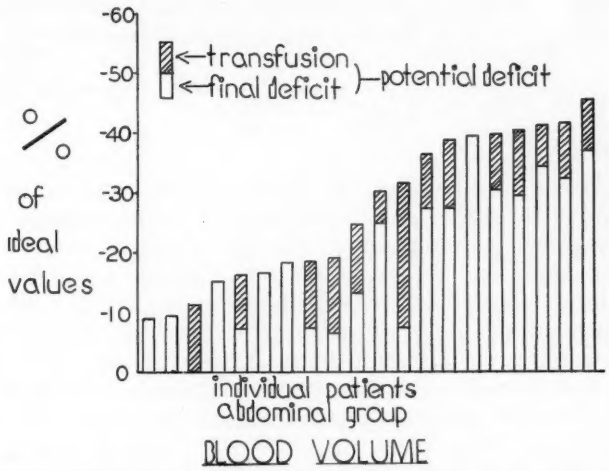


Fig. 3.—Potential and final deficits in blood volume of abdominal hysterectomy patients expressed in per cent of ideal values. Potential deficits equal the preoperative blood volume deficit plus operative blood loss exclusive of transfusion. Final deficits equal preoperative blood volume deficit plus operative blood loss in excess of transfusion. Patients are plotted in order of increasing potential deficits. The top of any bar is the potential deficit, and the cross-hatched areas represent transfusion replacements. The clear areas are the final deficits. If no transfusion was given, the potential and final deficits are identical.

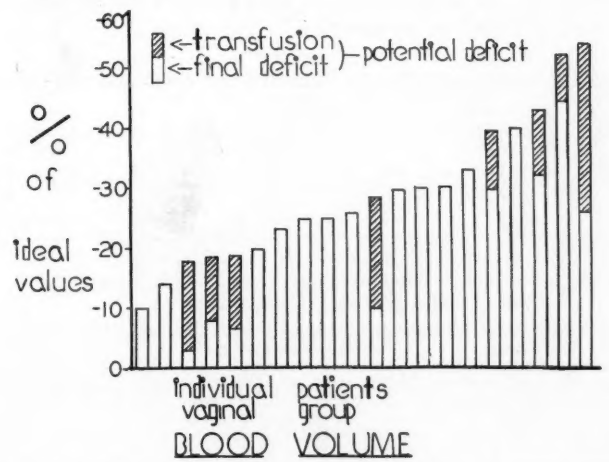


Fig. 4.—Potential and final deficits in blood volume of vaginal plastic patients expressed in per cent of ideal values. For explanation refer to Fig. 3.

For practical purposes the potential deficit was only theoretical. Because of either excessive operative blood loss or signs of approaching shock, transfusions were begun. In the abdominal group 14 patients required transfusions, 8 of whom had been permitted to progress to a stage of marked hypotension and tachycardia either during or after the operation. On the other hand, only 8 patients of the vaginal group required transfusions and 4 of these

showed some early signs of shock. Those transfusions altered the potential deficit so that the final deficit (preoperative blood volume deficit plus operative blood loss in excess of transfusion) averaged –19.6 per cent in the abdominal group and –23.1 per cent in the vaginal group, with a maximum of –39.2 and –44.4 per cent, respectively, below ideal values (Table III).

TABLE III. FINAL DEFICIT IN BLOOD VOLUME EXPRESSED IN PERCENTAGE OF IDEAL VALUES

	AVERAGE (%)	MAXIMUM (%)	MINIMUM (%)
Abdominal	-19.6	-39.2	-0.0
Vaginal	-23.1	-44.4	-2.7

If we examine Figs. 3 and 4 again, it appears that most of the patients with blood volume deficits in excess of –20 per cent in the abdominal group and –30 per cent in the vaginal group received blood. Perhaps these deficits are critical levels, but the sampling is too small to establish such a conclusion. Nevertheless, why should the deficits below ideal figures beyond which transfusion is given be lower in the abdominal than in the vaginal groups? Two reasons seem to be apparent. First, during hysterectomy, the peritoneal cavity is opened, and this maneuver drops the blood pressure enough to hasten shock. Second, and perhaps more important, patients enter the operating room with fewer red blood cells than those of the vaginal group. Figs. 5 and 6 and Tables IV and V demonstrate that, if we consider the red blood cell mass alone and not the blood volume, the final deficit in both groups with reference to the ideal figures is fairly similar. The deficits average –28 per cent and –26.3 per cent in the abdominal and vaginal groups, respectively. The proximity of these 2 averages is especially interesting since we tended to transfuse almost all patients in both groups who had potential deficits in red cell mass in excess of 30 per cent (Figs. 5 and 6). Perhaps then, red blood cell mass is a more suitable point of reference.

TABLE IV. POTENTIAL DEFICIT IN RED BLOOD CELL MASS EXPRESSED IN PERCENTAGE OF IDEAL VALUES

	AVERAGE (%)	MAXIMUM (%)	MINIMUM (%)
Abdominal	-35.9	-58.7	-9.1
Vaginal	-31.3	-59.2	-8.6

TABLE V. FINAL DEFICIT IN RED BLOOD CELL MASS EXPRESSED IN PERCENTAGE OF IDEAL VALUES

	AVERAGE (%)	MAXIMUM (%)	MINIMUM (%)
Abdominal	-28.0	-49.4	-4.9
Vaginal	-26.3	-51.3	-+0.4

Our interpretations up to now have been based on what Randall considers ideal levels for blood volume. Now we focus our attention on the clinically determined T-1824 blood volumes, forgetting about ideal values to try to ascertain what percentage of the known blood volume the operative blood loss is. Figures are constantly being quoted to indicate the percentage depletion in blood volume required to send a person into shock. Wiggers[10] quoting Baacher states that in a series of battle casualties blood volume depletion of 14.4 per cent did not result in shock, whereas 20.7 per cent, 34.3 per cent, and 45.9 per cent deprivation was followed by mild, moderate, and severe

shock, respectively. Wiggers goes on to generalize and states that a one-third loss in blood volume leads to moderate shock, and one-half loss is necessary for severe shock. Are these so-called limits of tolerance approached in this study?

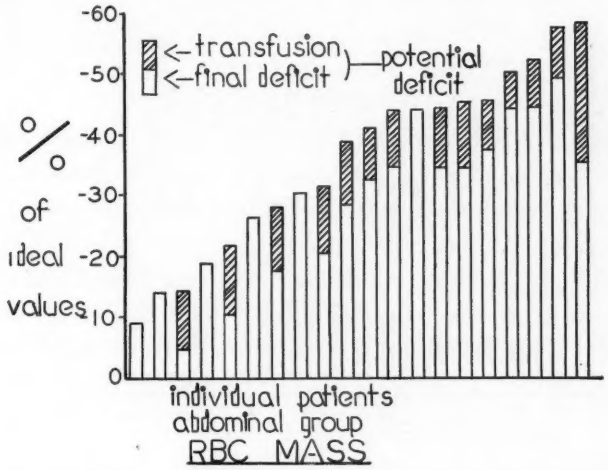


Fig. 5.—Potential and final deficits in red blood cell mass of abdominal hysterectomy patients expressed in per cent of ideal values. For explanation refer to Fig. 3.

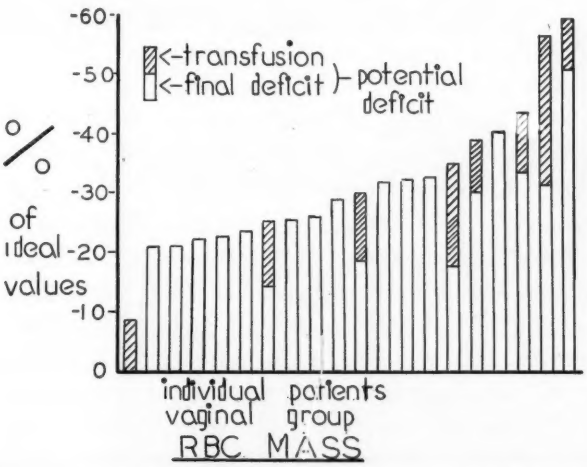


Fig. 6.—Potential and final deficits in red blood cell mass of vaginal plastic patients expressed in per cent of ideal values. For explanation refer to Fig. 3.

What percentage of loss in this series of known blood volumes could operative blood loss account for, and at what point did we transfuse the patients? Operative blood losses in both groups were similar to those found in a previous study.[8] Tables VI and VII and Figs. 7 and 8 indicate that in the vaginal group a top limit of about 14 per cent and in the abdominal group of 10 per cent depletion in blood volume was permitted without transfusion. Though the average potential deficit in the known blood volume in both groups was essentially the same, –13.1 per cent in the hysterectomy patients and –15.2 per cent in those who had vaginal repairs, reserve blood volume was evidently poorer in the abdominal group and therefore transfusion was more

frequent. The final deficit was only –3.6 per cent below the preoperative volume in the hysterectomy patients, whereas it was –8.6 per cent or double in the vaginal group. The blood losses did not even approach the limits quoted by Beecher, and we could have his figures and be much closer to the limits of tolerance for gynecological patients.

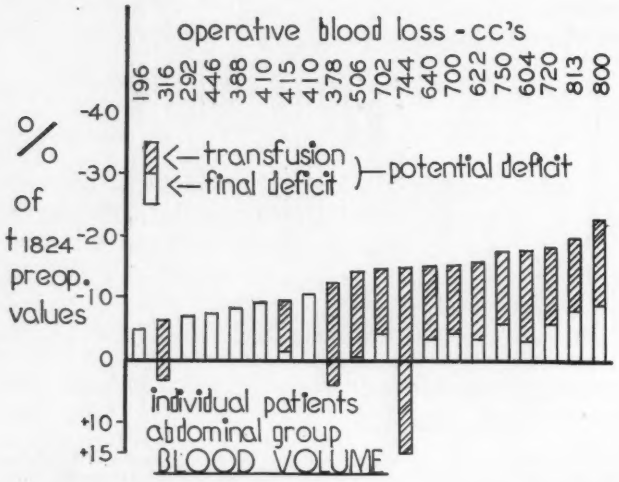


Fig. 7.—Potential and final deficits in blood volume of abdominal hysterectomy patients expressed in per cent of T-1824 determined blood volume values. The T-1824 values are those determined preoperatively. The deficit in these values is that produced by the blood loss at operation. Potential deficit is the total loss and final deficit is that in excess of replacement transfusion.

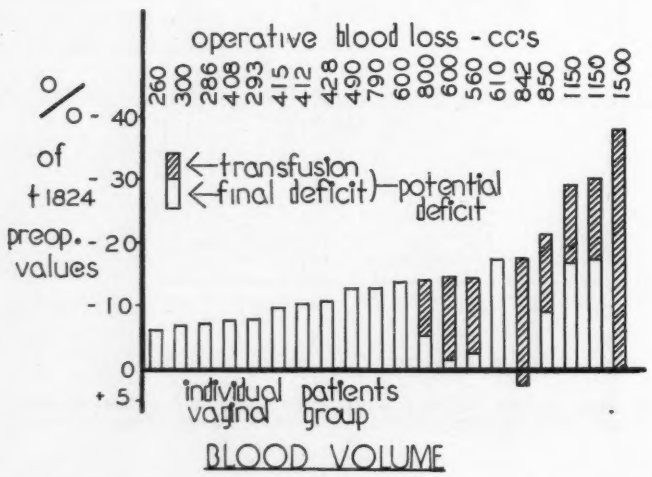


Fig. 8.—Potential and final deficits in blood volume of the vaginal plastic patients expressed in per cent of the T-1824 determined blood volume values. For explanation refer to Fig. 7.

TABLE VI. POTENTIAL DEFICIT IN THE T-1824 DETERMINED BLOOD VOLUME CAUSED BY OPERATIVE BLOOD LOSS

	AVERAGE (%)	MAXIMUM (%)	MINIMUM (%)
Abdominal	-13.1	-22.6	-4.8
Vaginal	-15.2	-38.0	-6.1

TABLE VII. FINAL DEFICIT IN THE T-1824 DETERMINED BLOOD VOLUME CAUSED BY OPERATIVE BLOOD LOSS

	AVERAGE (%)	MAXIMUM (%)	MINIMUM (%)
Abdominal	-3.6	-10.5	+15.3
Vaginal	-8.6	-17.3	+3.4

Comment

Wiggers,[11] one of the leading authorities on the subject of shock, recalled that his first observation of a patient in shock occurred as a medical student in 1905. The patient was a woman in her thirties who had undergone a hysterectomy and died of shock in the postoperative period. Shock was secondary to operative blood loss. Considerable progress has been made since 1905, and many therapeutic agents, not available then, may be obtained to combat the effects of blood loss. Transfusion is our most potent weapon, but in gynecology we use our subjective estimation and rely on experience to guide us in replacing blood volume deficits. This approach has been reasonably successful.

Our results indicate that many of our gynecological patients enter the hospital with a diminished blood volume. On one hand, the group of patients subjected to vaginal repairs enter with a deficit in both plasma volume and red blood cell mass which is roughly proportionate to the reduction in total blood volume. On the other, the candidate for hysterectomy is found to have a relatively greater deficit in red blood cells than plasma volume. The plasma compartment expands only partially to compensate for excessive loss in red blood cells, but the volume is not restored to normal thereby.

These deficits in blood volume are the results of bleeding from fibroids, adenomyosis, or carcinoma, or derangements in hemoglobin metabolism secondary to systemic diseases such as tuberculosis. The blood volume behavior of the patients dealt with in this paper parallels the findings in unselected groups of general surgical patients. Randall,[8] and Beling and associates[12] reported that 65 and 75 per cent, respectively, of their series of general surgical patients required one or more transfusions to replace the preoperative volume deficits. Beling and Clark and collaborators[13] commented specifically on the relatively greater deficits of erythrocytes as compared with plasma. This was the case in the abdominal group. Beling and Clark believed that carcinoma or other serious illness interfered with bone marrow hemoglobin metabolism so that the loss in red blood cells was not replaced as it should have been. The depletion in erythrocytes as well through hemorrhage in the female genital tract may be so considerable, and frequent enough to outdistance even the most active marrow. Hence, there is a dearth of red blood cells, while some of the plasma is replaced.

How are we to anticipate a lowered blood volume? We could do T-1824 blood volume determinations routinely, but this would not be practical. Preoperative cell volume may be of some help, but if we turn to Fig. 9, on which red blood cell mass expressed as per cent of the ideal value is plotted against

hematocrit, we find that we may be deceived very easily. There is no consistent correlation between the two. If the plasma volume were to expand to maintain a normal blood volume in the presence of a shrunken red blood cell mass, then anemia would be apparent. This is not so, however, because both compartments of the blood stream are depleted together (plasma usually not as much as the red blood cells). The hemoglobin and the hematocrit are dependent on the ratio of red blood cells to plasma and up to a variable but individually consistent point of red blood cell depletion the ratio is usually kept within relatively narrow limits. Clark[13] draws reference to the fact that other investigators found it impossible to restore plasma volume beyond a certain point in anemia where further attempt to return the blood volume to normal would only accentuate the anemia. He also points out that the type of anemia due to the loss of circulating hemoglobin favors the loss of fluid from the vascular to the intercellular compartment. Such a change will eventuate in the loss of tissue protein and tissue turgor and this in turn, in the presence of a lowered red blood cell mass, will increase the susceptibility to shock, and he labeled the syndrome chronic shock. Reserve spaces and capillaries are closed off to shrink the area through which blood must traverse in chronic shock and they will reopen when the erythrocytes are replaced.

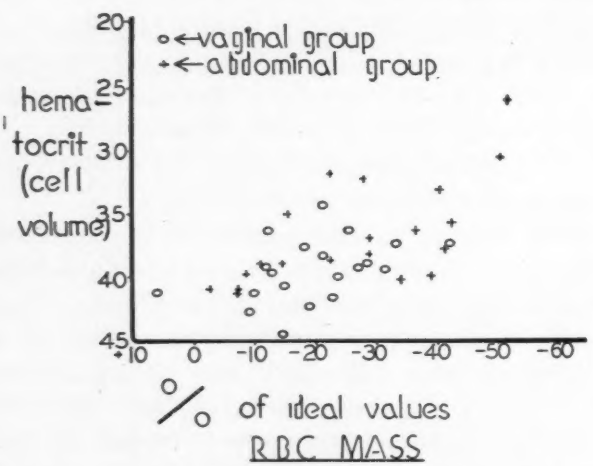


Fig. 9.—Scattergraph of the preoperative hematocrit and the red blood cell mass deficit expressed as per cent of the ideal values.

If we cannot truly rely on the preoperative hemoglobin or hematocrit, what clues can we use to guide us? Evidently the history of bleeding is more significant than the hemoglobin level and usually heralds a deficit in the red blood cell mass even in the presence of a relatively normal hematocrit. When we do find a markedly lowered hematocrit in addition to a history of bleeding, however, we should be all the more alert, for the combination of the two usually signifies a large deficit in the red blood cell mass.

The surgeon can expect a gynecological patient to lose an additional 600 c.c. of blood at the operation. If she were not transfused, she would enter the postoperative period 30 to 35 per cent below her ideal blood volume.

She may go as low as or even lower than –60 per cent of ideal volume. If she is not transfused when she goes below –25 to –30 per cent, she has a reasonably good chance of going into shock. The chances of shock are doubled in the patient undergoing abdominal hysterectomy and the need for preoperative transfusion is also greater than in the patient undergoing vaginal repair. The former group is usually in a poorer state of blood volume equilibrium, and in addition the peritoneal cavity is invaded. If we were to do blood volume determinations beforehand and check the margin of safety in blood loss, transfusion would be necessary at –10 per cent below the known T-1824 volumes.

Operative shock should be prevented rather than treated. From the results of this study it appears that shock can usually be averted if we transfuse patients who have a history of excessive bleeding for several months. The transfusion should be given to these patients preoperatively if the hematocrit is found to be below 35 per cent, or during operation before 400 c.c. of blood is lost, if it is above 35 per cent. Furthermore, the patient who has carcinoma, tuberculosis, or any chronic disease should be carefully evaluated and transfused preoperatively if necessary. On the other hand, if a patient is to undergo an elective procedure such as a vaginal plastic operation, she needs no special consideration until operative blood loss is in excess of 500 c.c.; then transfusion is necessary and the loss should be corrected. Finally, satisfactory control of blood volume demands some reasonably accurate measurements of operative blood loss.

Summary

1. The preoperative and operative blood volume levels of 40 gynecological patients were studied. One-half were admitted for and subjected to abdominal hysterectomy, and one-half for vaginal plastic operations. Total blood volume was determined by the Evans blue technique, and operative blood loss was measured by the gravimetric technique.

2. The following results were obtained and expressed in terms of ideal blood volume values:

A. Both vaginal plastic and abdominal hysterectomy patients had significant preoperative deficits in blood volume.

B. Large preoperative blood volume deficits of the abdominal hysterectomy patients were due primarily to a reduction in the red blood cell mass. The plasma compartment, though deficient in these patients, enlarged slightly to compensate for the deficit in total blood volume.

C. Preoperative blood volume deficits in the vaginal plastic patients were a combination of both deficient red blood cell mass and deficient plasma volume.

D. Preoperative blood volume deficit and operative blood loss together can reduce the blood volume to more than one-half of its ideal value.

E. Transfusion either before or during the operation was necessary if the blood volume deficit was greater than –20 per cent in the abdominal hysterectomy patients and –30 per cent in the vaginal plastic patients.

3. Using the blood volume determined by the Evans blue technique as a base line, an operative blood loss in excess of 10 per cent of the determined blood volume of the hysterectomy patients, and 14 per cent of the vaginal plastic patients necessitated replacement transfusions.

4. Twice as many abdominal hysterectomy patients required transfusions as did vaginal plastic patients.

5. Preoperative hematocrits did not furnish a reliable index of the blood volume status of the gynecological surgical patient. However, the history of bleeding prior to operation usually heralded a diminished blood volume.

6. It is believed that the patient who has bled excessively for several months should usually be transfused. Transfusion should be administered in these patients preoperatively if the hematocrit is below 35 per cent, or operatively before 400 c.c. is lost, if it is above 35 per cent.

7. Blood loss in excess of 500 c.c. in any patient should be corrected by transfusion.

8. Measurement of operative blood loss is an extremely valuable aid in management.

References

1. Soutter, Lamar: in Meigs, J. V., and Sturgis, S. H., editors: Progress in Gynecology, New York, 1950, Grune & Stratton, p. 762.
2. Gregerson, M. I.: J. Lab. & Clin. Med. **29**: 1266, 1944.
3. Brady, L. W., Cooper, D. Y., Colodzin, M., McClenathan, J. E., King, E. R., and Williams, R.: Surg., Gynec. & Obst. **97**: 25, 1953.
4. Berlin, N. I., Hyde, G. M., Parsons, R. J., and Lawrence, J. H.: New England J. Med. **247**: 675, 1952.
5. Baronofsky, I., Treolar, A., and Wangensteen, O.: Surgery **20**: 761, 1946.
6. Stanton, J. R., Lyon, R. P., Freis, E. D., and Smithwick, H.: Surg., Gynec. & Obst. **89**: 181, 1949.
7. Randall, H. T.: Personal communication.
8. Randall, H. T.: S. Clin. North America **32**: 3, 1952.
9. Buchman, M. I.: Am. J. Obst. & Gynec. **65**: 53, 1953.
10. Wiggers, C. J.: Physiology of Shock, New York, 1950, The Commonwealth Fund, p. 40.
11. Wiggers, C. J.: Physiology of Shock, New York, 1950, The Commonwealth Fund, p. 29.
12. Beling, C. A., Bosch, D. T., and Morton, T. V., Jr.: Surg., Gynec. & Obst. **90**: 686, 1950.
13. Clark, J. H., Nelson W., Lyons, C., Mayerson, H. J., and DeCamp, P.: Ann. Surg. **125**: 618, 1947.

FATAL CARCINOMA OF THE CERVIX

A Study of 58 Autopsies

P. J. Bartzen, M.D., Duluth, Minn., and W. F. Hovis, Jr., M.D., and D. J. Albrecht, M.D., Milwaukee, Wis.

(From the Departments of Obstetrics and Gynecology, Milwaukee General Hospital, and Marquette University Medical School)

ONE learns best by studying mistakes. Prompted by this axiom we studied the autopsy material of 58 patients who died with carcinoma of the cervix at Milwaukee County Hospital from January, 1942, until January, 1954. We felt that perhaps a significant number might have had what we consider good therapy and died in spite of it, although, after sifting the material we found that there were too few patients, especially in Stages I and II (International) who had had adequate therapy (only 10). Therefore, we were unable to evaluate fully our own treatment in these relatively few cases. However, a number of interesting facts came to light.

We have had too little experience with radical surgery for recurrent or radioresistant carcinoma of the cervix to have formed an opinion regarding its place in our armamentarium. Although we are not specifically looking for it, an implication arises from this study that seems to support the radical surgery enthusiast.

Material

The autopsy and clinical records of 58 patients were studied in detail. New sections of pancreas, heart, and parametria were cut in several instances to check uremia as the cause of death when the clinical charts lacked recent enough blood studies.

The clinical records were plotted for temperature curve, clinical stage at diagnosis, months from diagnosis to death, character of death (respiratory, etc.), body weight, and laboratory work, including nonprotein nitrogen, urine, and blood examinations.

An analysis of the charts of 134 patients who died with carcinoma of the cervix in the same period of years but were not autopsied was done as well. The conclusions derived from this latter study were for the most part corroborative, and will not be included in this paper. When dealing with causes of death, conclusions based on clinical charts alone are inaccurate.

Results

1. Causes of Death.—Table I lists the causes of death. If uremia and pyelonephritis are combined, as some authors prefer, the deaths from "renal causes" number 23 (39.6 per cent). It will be noted that uremia was three times as common as any other cause.

Of the 8 patients who died of intercurrent disease, 6 would have gone on to die of their disease at a later date. The 2 who died with no evidence of carcinoma had acute pancreatitis and lobar pneumonia, respectively.

The group labeled "multiple factors" has been called "cachexia," "anemia and cachexia," or "unknown" by other authors. The average body

weight at death in our multiple factors group was 96.2 pounds. Their average hemoglobin determination just prior to death was 37 per cent compared to an average last hemoglobin determination of the entire series, which was 57 per cent. We are unable to explain such a manifest effect by the mere presence of tumor. Three "multiple factor" patients had no significant pathology at postmortem other than a moderate amount of pelvic tumor; and another, small metastatic liver lesions.

TABLE I. AUTOPSY FINDINGS, 58 PATIENTS, MILWAUKEE COUNTY HOSPITAL

CAUSE OF DEATH	NO.	PER CENT
Uremia	20	34.8
Unrelated cause	8	13.7
Multiple factors	7	12.0
Death from pulmonary metastatic lesion	5	8.6
Peritonitis	4	6.9
Pyelonephritis	3	5.2
Pelvic abscess	3	5.2
Bowel obstruction due to tumor	2	3.5
Bowel perforation due to tumor	2	3.5
Septicemia	1	1.7
Postoperative death	1	1.7
Cerebrovascular accident (due to tumor)	1	1.7
Hemorrhage	1	1.7
Total	58	100

2. Ureteral Compression.—It seems that, since carcinoma of the cervix metastasizes late and invades laterally early, more patients would die of uremia. There was the expected incidence of ureteral compression as a purely anatomic finding (Table II). This is in keeping with the findings in similar studies by many authors, notably Henriksen.

TABLE II. URETERAL COMPRESSION

	PEARSON	BRUNSCHWIG	HENRIKSEN	THIS SERIES
Evidence of ureteral compression	75%	63%	80%	69%
Death from uremia and/or pyelonephritis	33%	28%	54%	39%
Number of autopsies	57	65	356	58

3. Cause of Death in Relation to Therapy.—Stimulated by Brunschwig and Pierce's paper, we checked the therapy given all 58 patients. By necessity, the 8 deaths from intercurrent disease were eliminated. An arbitrary minimum therapy was designated in order to obtain two distinct categories: "adequate" and "inadequate." Most of the patients who fell into the "inadequate treatment" group (see Table III) had palliative or no therapy. The planned therapy for all cases in which a cure was the aim was far in excess of our "minimum." We chose the lesser figure since a few clinics approximate this dosage as their optimum.

The "died of local disease" category in Table III represents those who died as a direct result of cancer in the pelvis or via contiguous spread to abdominal organs. We would normally expect a higher percentage of deaths due to local disease among untreated patients, and conversely, expect a higher percentage of deaths from metastases among the treated patients. The two groups are nearly identical. Apparently, whether the patient receives adequate treatment, partial treatment, or no treatment, the character of her death is the same.

TABLE III. CAUSE OF DEATH IN RELATION TO THERAPY

CAUSE OF DEATH	ADEQUATE THERAPY NO. OF CASES	INADEQUATE THERAPY* NO. OF CASES
Local spread of disease	10 (91%)	33 (85%)
Distant metastasis	1 (9%)	6 (15%)
Total†	11	39

*Arbitrary minimum therapy for this study:
Radium—4,500 mg. hr. (some intracavitary).
X-ray—Total 6,000 r in air to at least 2 ports.
†Does not include deaths from intercurrent disease.

4. Node and Organ Involvement.—The percentage of cases with some node involvement was 62.5 per cent. Only those cases in which nodes were identified, removed, and proved positive for tumor by section are included. There were another 10 patients, however, who we suspect may have had node cancer via lymphatic spread. In each of these, the pelvic tumor exceeded 10 cm. in diameter, and at least parametrial and ureteral nodes were destroyed beyond recognition. We cannot be sure, however, that the nodes were not just enveloped as the cancer spread into the parametrium. If, in each of the 10 instances, there had been lymph channel spread to nodes, the percentage of involvement for the entire series would have been about 80 per cent. This seems extremely high.

Primary nodes have been described as the ureteral, parametrial, hypogastric, external iliac, and obturator; secondary, as the common iliac, superficial and deep inguinal, and the aortic as high as the diaphragm; and the distant nodes as any beyond those limits.

TABLE IV. DISTRIBUTION OF NODE INVOLVEMENT

SITE	THIS SERIES		HENRIKSEN	
	TREATED	UNTREATED	TREATED	UNTREATED
Primary nodes	64%	54%	58%	44%
Secondary nodes	64%	50%	70%	39%
Distant organ	46%	59%	38%	32%
Number of autopsies	58		350	

Table IV has "distant organ" where it appears that "distant node" belongs. This is due to the fact that in every instance where a distant node was found containing carcinoma a distant organ with metastasis was found as well. The converse was not true. There were 3 cases in which a distant organ was involved but no positive nodes were found except in the pelvis.

We saw an exceptionally high percentage of involvement of the adrenal gland (14 per cent), kidney (14 per cent) and spleen (9 per cent). The highest figures that were found for any of the three organs in the literature were 2 to 3 per cent. We are at a loss to explain this.

5. Disease Confined to the Pelvis.—Three patients had no residual carcinoma, and another had an early Stage I lesion discovered for the first time at postmortem. Of the remaining 54 patients, 24 (44.4 per cent) died with their carcinoma limited to the pelvis. In hindsight, there were not 24 potential candidates for radical surgery, however. Twelve were poor risks due to heart disease, severe anemia and cachexia, age, etc. This left 12 (22.2 per cent) who might have been considered for radical surgery.

Review of Literature

Table V gives a breakdown of the most recent papers written on this subject. The total of 613 cases and the averages thereby obtained seem significant. Note that the oft-quoted triad of "uremia—infection—hemor-

rhage'' forms only 65 per cent of the total. Some claim that we have hemorrhage well controlled by virtue of adequate blood replacement and hypogastric ligation, and that infection can be combated adequately with antibiotics (despite repeated demonstration of bacterial adaptations). This allegedly leaves only renal complications to combat. The 35 per cent who succumb to causes other than the triad speaks against oversimplifying the problem of carcinoma of the cervix.

TABLE V. CAUSES OF DEATH FROM CARCINOMA OF CERVIX (SINCE 1933)

AUTHOR	NO. OF CASES	RENAL DISEASE*	PERITONEAL SEPSIS†	HEMORRHAGE	PULMONARY DIS.‡	SEPTICEMIA	BOWEL OBSTRUCTION	CACHEXIA, ETC.	INTERCURRENT DISEASE
Pearson	57	37%	19%	9%	4%	0	4%	9%	5%
Auster and Sala§	142	28%	28%	8%	8%	23%	1%	3%	1%
Behney	166	21%	3%	9%	26%	9%	6%	22%	4%
Brunschwig and Pierce	65	28%	28%	0	6%	11%	5%	0	6%
Ward, Sellers, and Davis	70	54%	6%	11%	0	?	4%	13%	0
DeAlvarez	55	40%	9%	2%	31%	0	13%	0	2%
This series	58	40%	16%	2%	9%	2%	4%	12%	14%
Total average	613	35%	16%	6%	12%	8%	5%	8%	5%

*Uremia and/or pyelonephritis.
†Includes pelvic abscess.
‡Includes septic pneumonia.
§Quoted from Behney.

Conclusion

1. In this series there are no striking differences in the cause and manner of death between the treated and untreated cases of carcinoma of the cervix.
2. No matter what the cause of death, an extremely high percentage of lymph node involvement is seen (62 to 80 per cent).
3. Roughly, one-half of the patients died with their carcinoma limited to the pelvis. One-half of these, or approximately one-fourth of the total, might have been considered for radical surgery.
4. Radiation therapy per se caused no deaths.

References

Aldridge, C. W., and Mason, J. T.: AM. J. OBST. & GYNEC. 60: 1272, 1950.
Behney, C. A.: Discussion of Morton and Dignam.
Brunschwig, Alexander, and Pierce, Virginia: AM. J. OBST. & GYNEC. 56: 1134, 1948.
Brunschwig, Alexander: Personal communication.
DeAlvarez, R. R.: AM. J. OBST. & GYNEC. 54: 924, 1947.
DeAlvarez, R. R.: West. J. Surg. 61: 623, 1953.
Drexler, L. S.: AM. J. OBST. & GYNEC. 57: 391, 1949.
Everett, H. S.: Gynecological and Obstetrical Urology, Baltimore, 1944, Williams & Wilkins Company.
Ewing, J.: Neoplastic Diseases, ed. 4, Philadelphia, 1940, W. B. Saunders Company.
Graves, R. C., Kickham, C. J. E., and Nathanson, I. T.: J. Urol. 36: 618, 1936.
Henriksen, Erle: AM. J. OBST. & GYNEC. 58: 924, 1949.
Herger, C. C., and Schreiner, B. F.: Surg., Gynec. & Obst. 43: 740, 1926.
Meigs, J. V.: AM. J. OBST. & GYNEC. 49: 542, 1945.
Morton, D. G.: In Meigs, J. V., and Sturgis, S. H., editors: Progress in Gynecology, New York, 1950, Grune & Stratton, Vol. II.
Morton, D. G., and Dignam, William: AM. J. OBST. & GYNEC. 64: 999, 1952.
Pearson, Bjarne: Am. J. Cancer 28: 31, 1936.
Sampson, J. A.: Bull. Johns Hopkins Hosp. 13: 299, 1902.
Sampson, J. A.: Bull. Johns Hopkins Hosp. 15: 156, 1904.
Taussig, F. J.: AM. J. OBST. & GYNEC. 45: 733, 1943.
Ward, S. V., Sellers, T. B., and Davis, J. T.: AM. J. OBST. & GYNEC. 63: 989, 1952.
Warren, S.: Arch. Path. 12: 783, 1931.

TOTAL PNEUMONECTOMY FOR METASTATIC UTERINE SARCOMA

CARL DAVIS, JR., M.D., CHARLES R. KEE, M.D.,* AND RICHARD H. ANDRESON, M.D., CHICAGO, ILL.

(From the Department of Surgery and the Department of Obstetrics and Gynecology, the Presbyterian Hospital and the University of Illinois College of Medicine)

BECAUSE of the infrequency of similar reports in the literature, a case is presented of a 61-year-old patient who eleven years earlier was treated elsewhere for a sarcoma of the uterus. Her recent illness concerned a presumed metastatic lesion to the right lung. There is no apparent evidence of recurrence since total pneumonectomy twenty-one months ago.

Case Report

Miss A. A., aged 61 years, was admitted to the Presbyterian Hospital, Chicago, on March 22, 1953, for treatment of a "tumor" or "some abnormality" in the right lung, discovered by an x-ray mobile unit in October, 1952. Some weeks before admission the patient had been treated for a lung infection. Fever and hemoptysis were present, but no dyspnea. An 8 pound loss of weight was noted in six months. A relevant fact in the past history was that the uterus had been removed about eleven years previously for "fibroids."

The patient was not acutely ill. The temperature, pulse, and respiration were normal; the blood pressure was 150/80 mm. Hg. Pertinent physical findings were confined to the chest and abdomen. There were decreased breath sounds with dullness over the upper half of the right lung field; no râles or friction rub were heard. The heart was not enlarged. A systolic murmur was present over the aortic area. An old midline lower abdominal celiotomy scar was observed. No abdominal masses were palpable. Vaginal examination could not be done because of a stenosed introitus. Rectal examination was negative.

The laboratory studies showed a hemoglobin level of 11.5 Gm. per 100 c.c., 3.7 million erythrocytes per cubic millimeter, and 12,300 leukocytes per cubic millimeter. Urinalysis was negative. Sputum examination revealed no acid-fast organisms. Roentgen examination of the chest was reported to show a lobular tumor mass involving the posterior and mid-portions of the right upper lung. This had the appearance of a benign tumor and its location and contour suggested neurofibroma (Fig. 1, *A* and *B*). Fluoroscopy of the chest with a barium swallow suggested a soft-tissue mass occupying the upper third of the right chest. The esophagus was deviated slightly to the left. Fluoroscopy of the stomach and duodenum showed a diverticulum, 3 cm. in diameter, arising from the junction of the second and third portions of the duodenum. No gross defects were found in the colon. The electrocardiogram was within normal limits.

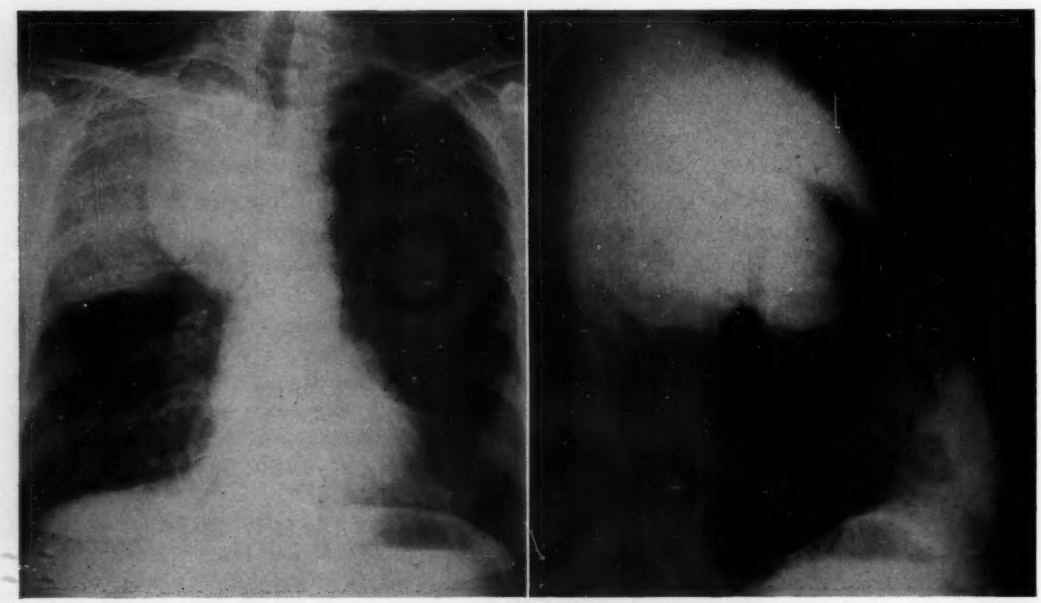
The bronchoscopy findings were as follows: "Both vocal cords move readily. There is an extrinsic mass pressing on the right lateral wall and the dorsal aspect of the lower trachea and the proximal portion of the right main bronchus. The coryna is sharp and pulsates. The right upper, middle, and lower lobe orifices are normal."† Examination of the fluid from the bronchus showed no malignant tumor cells. The impression was a mediastinal mass with compression of the lower trachea and right main bronchus.

---

*Kee-Dehlin Clinic, Gladstone, Mich. Dr. Kee is now serving in the Medical Corps, United States Navy, Newport News, Va.

†Bronchoscopy by Stanton A. Friedberg, M.D., Chairman, Department of Oto-Laryngology, the Presbyterian Hospital, Chicago, Ill.

Operation.—Anesthesia was induced with Pentothal sodium. Intratracheal ether and nitrous oxide were administered. The right chest was opened through the bed of the fourth rib. No free fluid was present. Thin fibrinous and fibrous adhesions bound the upper lobe to the parietal pleura. The upper lobe of the right lung was consolidated and contained a tumor. Biopsy of one mediastinal lymph node showed no evidence of tumor on frozen section. A total pneumonectomy was performed (C. D., Jr.). Inasmuch as the postoperative course was without incident, the patient was discharged from the hospital on the thirteenth day of convalescence. No roentgen therapy was given.



A. *B.*

Fig. 1.—*A,* There is an oval-shaped density in the right upper lung field.
B, Lateral roentgenogram of the chest illustrates atelectasis in the upper lobe with the tumor mass lying anteriorly.

Pathology (Gross).—The entire right lung was presented as a gross specimen. The external surface of the upper lobe was irregular due to shaggy adhesions. The lobe was firm thoughout, while the middle and lower lobes were crepitant. A firm, smooth tumor mass involved the lower half of the upper lobe. On the cut surface there was a distinct, somewhat kidney-shaped, solid, tan tumor 9.0 by 6.0 by 7.0 cm. (Fig. 2). The neoplasm was compressing the pulmonary vessels and bronchioles. The rest of the lobe was airless, reddish brown and gray, and suggested the picture of an old unresolved pneumonic process. The pulmonary parenchyma of the other lobes was unaltered except for the presence of a brown nodule, 2 cm. in diameter, in the middle lobe, while in the lower lobe there were two subpleural nodules, 0.5 cm. in diameter. These latter two resembled the main tumor.

*Pathology (Microscopic).**—The tumor of the upper lobe (Fig. 3, *A*) was composed of compactly arranged spindle-formed cells, showing a moderate degree of variation in size and shape with considerable variability in the size of the nuclei so that the basic histology was that of a fibrosarcoma. The tumor was replacing pulmonary structure and invading along the trabecular groups where it had isolated bronchi and peribronchial structures. Frequently blood vessels in the area of tumor showed thrombosis with organization but there was no evidence of tumor cells in the blood vessels. There were extensive areas of myxomatous degeneration and hyalinization in the tumor. Sometimes these

* Submitted by Gordon Vawter, M.D., the Department of Pathology, the Presbyterian Hospital, Chicago, Ill.

were associated with calcification and even bone formation. In other areas there was acute necrosis with heavy neutrophilic leukocytic infiltrates. There were also large areas of hemorrhage in the tumor. The tumor grew closely under the pleura. The associated pulmonary parenchyma showed atelectasis.

There was one section of the middle lobe of the lung showing atelectasis, parenchymal fibrosis, and a low-grade chronic pneumonitis characterized principally by macrophagic infiltrates. This was nonspecific in character. There was no evidence of tumor.

There were two sections of the lower lobe of the lung. One showed a focal area of atelectasis, fibrosis, and low-grade pneumonitis similar to that found in the middle lobe. A second section (Fig. 3, *B*) of the lower lobe showed a nodule beneath the pleura composed of walls of highly vascular, spindle-formed cells with cigar-shaped nuclei.

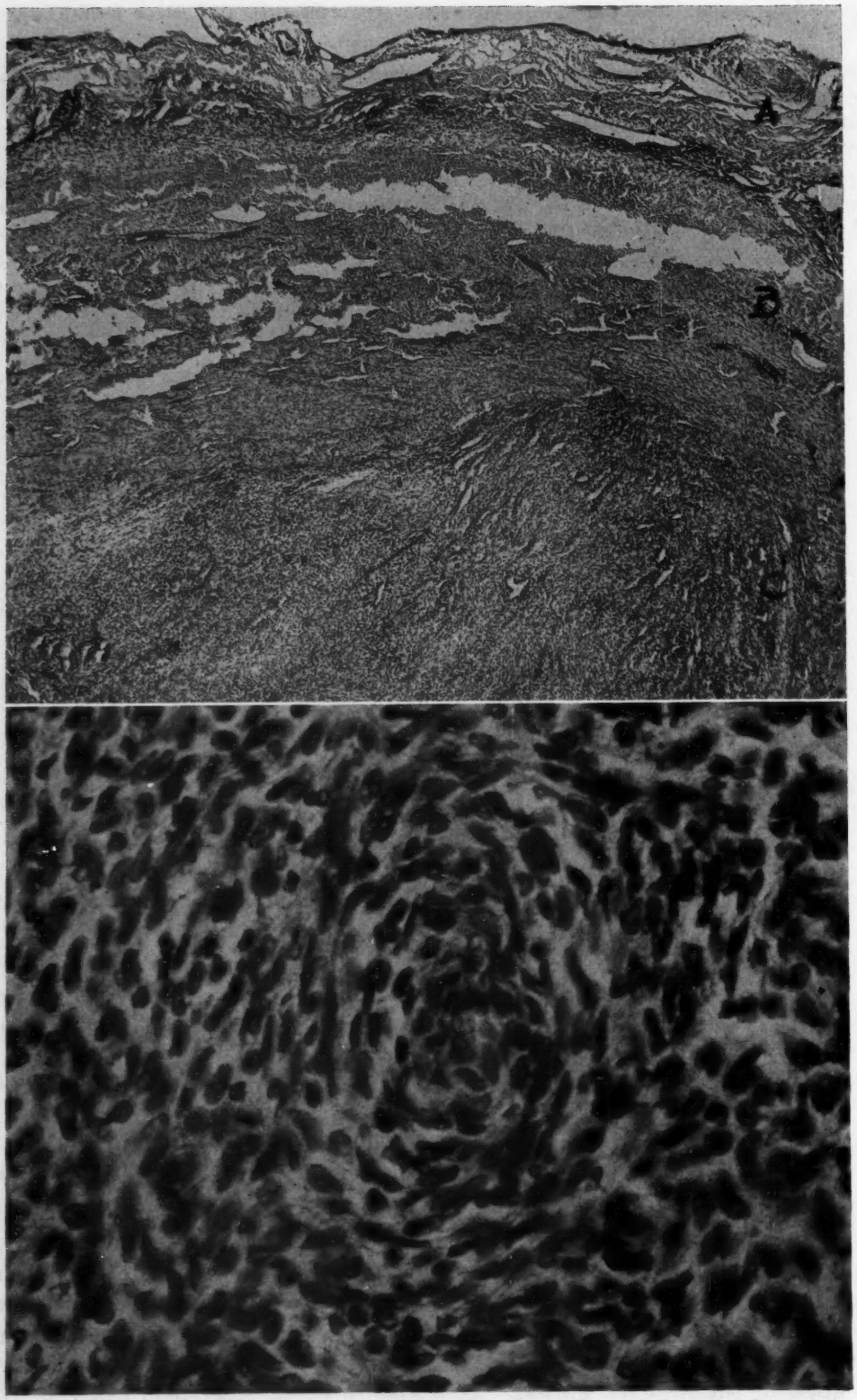
Fig. 2.—Photograph of the cut surface of the upper lobe, illustrating the tumor.

Impression.—Although the original specimen submitted from the uterus (Fig. 4, *A* and *B*) was diagnosed as a leiomyosarcoma, the tissue obtained from the lung neoplasm was composed of spindle-formed cells which resembled in parts a fibrosarcoma, while in other regions, a leiomyosarcoma.

Comment

With increased frequency, thoracic surgeons are requested to perform pulmonary resections upon patients with solitary metastatic lesions many months, often years, after removal of a primary tumor. Only fourteen years ago, Churchill[1] wrote: "The status of pulmonary resection for known metastatic tumors of the lung is admittedly one of experimentation. In general, it may be taken under consideration when a solitary metastasis of a tumor of relatively low-grade malignancy appears in the lung after complete eradication of the primary growth. It is also to be considered in cases of hypernephroma with a solitary pulmonary metastasis." Alexander and Haight,[2] as well as Effler and Blades,[3] have discussed the indications and procedures for

A.

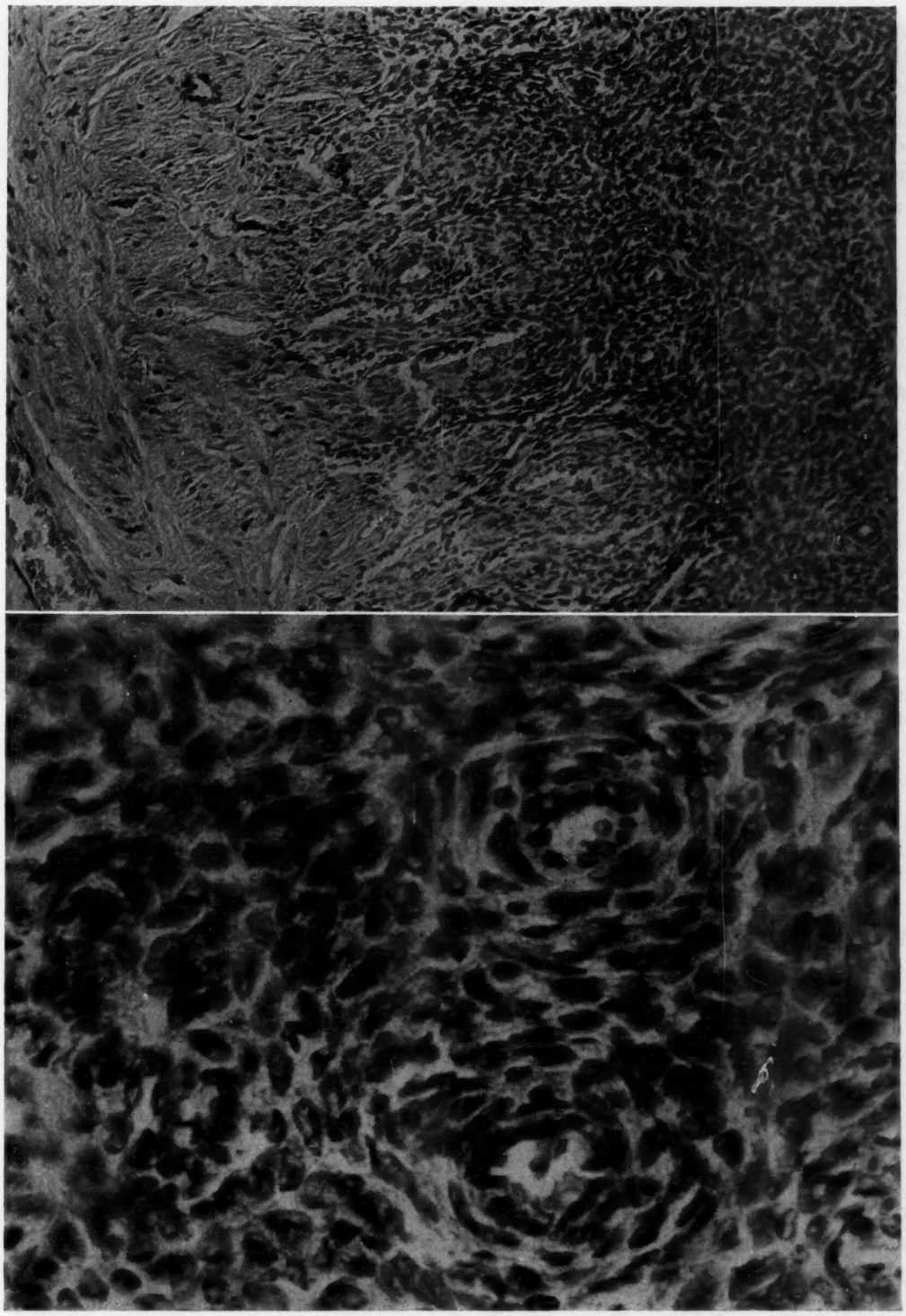


B.

Fig. 3.—*A*, Low-power photomicrograph of a section of the upper lobe, showing (*A*) pleura, (*B*) atelectatic, fibrotic, and hemorrhagic pulmonary parenchyma, and (*C*) tumor infiltration.

B, High-power photomicrograph of section of one of the two small tumor nodules in the lower lobe of the lung—a lesion histologically indistinguishable from that shown in Fig. 4, *B*.

A.



B.

Fig. 4.—*A*, Medium-power photomicrograph showing the intimate relationship between myometrium and tumor. (Original section of uterus, courtesy of Dr. R. L. Troup.)

B, High-power photomicrograph of the uterine tumor, showing a densely cellular neoplastic process with little stroma. The spindle-shaped cells of the neoplasm, which show moderate amounts of cytoplasm and irregularly staining nuclei, form tight whorls.

surgical removal of a presumed solitary metastatic neoplasm in the lung and have presented case reports pertinent to this subject. Recently, Seiler, Clagett, and McDonald[4] of the Mayo Clinic reviewed the literature concerning surgical excision of isolated metastatic pulmonary lesions and added ten cases of their own. Through the years isolated cases with a solitary pulmonary metastasis, treated by local resection, lobectomy, or pneumonectomy, have been reported. The site of the primary tumor has shown considerable variation.

In the literature there are only a few reports concerned with the treatment of an isolated pulmonary metastasis secondary to sarcoma or carcinoma of the uterus. In 1930, Torek[5] removed a metastatic adenoacanthoma of the lung two years and eight months after complete hysterectomy for the primary neoplasm. In 1933, Lilienthal[6] reviewed a case of pneumonectomy performed for removal of a tumor of the left lung which proved to be metastatic from a sarcoma of the uterus. The primary lesion was found at autopsy. In 1942, Brezina and Lindskog[7] described a case of total right pneumonectomy for a metastatic lesion from a primary carcinoma of the uterus. Thirteen years previously a subtotal hysterectomy and bilateral salpingo-oophorectomy had been performed for postmenopausal bleeding. In 1950, Seiler, Clagett, and McDonald reported a pneumonectomy for a solitary metastasis in the lung secondary to adenocarcinoma of the uterus. In a recent discussion of the treatment of secondary tumors of the lung, Kergin[8] reported a three-year survival period following removal of an isolated pulmonary metastasis secondary to acanthoadenocarcinoma of the uterus. He indicated that almost every type of tumor which is capable of metastasizing to the lung has been treated by pulmonary resection and that the sarcomas appear to have given a little better results than the carcinomas.

In the review of 62 cases by Seiler and his associates, bronchial involvement was noted in 17 cases of secondary pulmonary infiltration; of this number there was a positive biopsy on bronchoscopy in 10 instances. King and Castleman[9] emphasized, after autopsy studies, that not all patients with symptoms of hemoptysis and bronchial occlusion were suffering from a primary neoplasm, but rather were found to have secondary metastasis. In the case reported herein, the apparent obstruction to the main bronchus of the right upper lobe resulted in atelectasis and pneumonitis. No intrinsic tumor was demonstrated at bronchoscopy. As a result of the compression of the trachea and the right main bronchus by a presumed extrinsic mass, a mediastinal tumor was considered, and an earlier impression of bronchogenic neoplasm dismissed.

There was no question concerning the previous hysterectomy for removal of fibromyomas until a review of the histological material from the lung suggested a sarcoma and the possibility of a secondary growth rather than a primary neoplasm. Inasmuch as primary sarcoma of the lung is a lesion of considerable rarity,[10, 11] further inquiry disclosed that the patient had been operated upon for sarcoma of the uterus. The reply was as follows: "Examination showed that the patient had a tumor the size of a seven months' pregnancy that extended almost as high as the xiphoid. On April 21, 1942,

a subtotal hysterectomy was performed. The pathological report stated that the specimen consisted of a large uterus, 22 by 15 by 14 cm. The uterus weighed 2,400 grams and was the seat of an extensive sarcoma. The microscopic diagnosis was extensive leiomyosarcoma of the uterus." (Fig. 4, *A* and *B*.)

It is interesting that approximately 11 years elapsed before there was apparent evidence of recurrence of sarcoma to the right lung; it is more amazing when one considers the degree of enlargement of the uterus by the original extensive sarcoma. Danforth[12] has indicated that sarcoma of the uterus may vary from a slowly growing tumor to one of extreme malignancy and rapid growth. This variation in malignancy may account for the late development of metastases in this case. In 1950, Finn[13] reported that only 7 out of 26 patients treated for uterine sarcoma by hysterectomy survived from five to seventeen years.

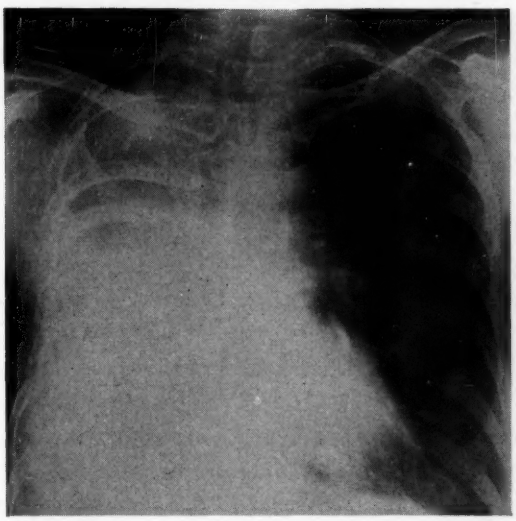


Fig. 5.—Roentgenogram of the chest 21 months after pneumonectomy. There is no apparent evidence of recurrence at this time.

Summary

A report is cited of a patient with sarcoma presumedly metastatic to the lung. Treatment consisted of total pneumonectomy. Approximately 11 years earlier a huge sarcoma of the uterus had been treated elsewhere by subtotal hysterectomy. At the present time, 21 months after pneumonectomy, the patient is apparently well without demonstrable evidence of further recurrence (Fig. 5). Although the prognosis is still in doubt, this experience tends to indicate that when a primary tumor has been apparently removed completely and when there is no evidence of metastatic spread other than a solitary metastasis to the lung, pneumonectomy or lobectomy has merit, either in prolonging life, or as a palliative procedure to add to the patient's comfort for the remaining months or years of life.

Addendum.—This patient was examined Oct. 20, 1955, and found to be in good general health. She has no complaints. A roentgenogram of the chest was negative for any apparent metastasis.

We wish to express our appreciation to Dr. R. L. Troup of Greenbay, Wisconsin, for the data supplied to complete the case history, for the opportunity of reviewing the early roentgenograms of the chest as well as the histological material from the uterus.

References

1. Churchill, E. D.: Surgery **8**: 961, 1940.
2. Alexander, J., and Haight, C.: Surg., Gynec. & Obst. **85**: 129, 1947.
3. Effler, D. B., and Blades, Brian: J. Thoracic Surg. **17**: 27, 1948.
4. Seiler, H. H., Clagett, O. T., and McDonald, J. R.: J. Thoracic Surg. **19**: 655, 1950.
5. Torek, Franz: Arch. Surg. **21**: 1416, 1930.
6. Lilienthal, H.: J. Thoracic Surg. **2**: 600, 1932-1933.
7. Brezina, P. S., and Lindskog, G. E.: J. Thoracic Surg. **12**: 728, 1943.
8. Kergin, F. G.: Surg., Gynec. & Obst. **99**: 115, 1954.
9. King, D. S., and Castleman, Benjamin: J. Thoracic Surg. **12**: 305, 1943.
10. Black, H.: J. Thoracic Surg. **19**: 655, 1950.
11. Watson, W. L., and Anlyan, A. J.: Cancer **7**: 250, 1954.
12. Danforth, W. C.: Proc. Inst. Med. Chicago **17**: 261, 1948-1949.
13. Finn, W. F.: Am. J. Obst. & Gynec. **60**: 1254, 1950.

122 South Michigan Avenue (Dr. Davis)

THE USE OF THE MALE TOAD TEST IN THE INVESTIGATION OF HYDATIDIFORM MOLE AND CHORIONEPITHELIOMA

RHODA M. ALLISON, M.D., LEEDS, ENGLAND

(From the Department of Pathology, The Huddersfield Royal Infirmary)

INTEREST in the hydatidiform mole reaches back into antiquity. The condition was known to Hippocrates, and Aëtius (1567) described small bladder bodies in the uterus associated with suppression of the menses.

In contrast, references to chorionepithelioma reach back barely a lifetime. Sänger (1889) first described this condition, but thought that it was a sarcoma of the uterus, a view held widely in England until well into the twentieth century. In particular the tumors were supposed to be of decidual origin and were designated "deciduoma malignum." The problem was finally unraveled by Marchand in Germany (1895), who recognized its origin in placental tissue, and renamed it chorionepithelioma.

The investigation and diagnosis of hydatidiform mole and chorionepithelioma by biological assay of the gonadotrophin in the urine are of comparatively recent origin. Professor Zondek, soon after the establishment of the Aschheim-Zondek test (1928), using the mouse as the test animal, investigated these conditions extensively and published his well-known papers on this subject in 1937 and in 1942. Since then many workers have repeated his work, using the same and other test animals, such as the rat, the rabbit, and the female toad, *Xenopus leavis.*

The present paper records the investigation of 14 cases of hydatidiform mole and 7 cases of chorionepithelioma, using the male toad and frog as the test animals. Although it is not claimed that anything new has been found in these investigations, nevertheless it is hoped that the test, with its now well-recognized attributes of simplicity, accuracy, and above all of rapidity, is admirably suited to the investigation of the chorionic gonadotrophin content of the blood serum, urine, and abnormal tissues; further, that such investigations can easily be undertaken by any general hospital laboratory staff.

Methods

The test animals used were English male toads, *Bufo bufo;* Asian green toads, *Bufo viridis;* and French male frogs, *Rana esculenta.*

The test procedure is as follows: Two healthy animals are chosen, and rinsed in cold water, the only toilet necessary, and placed in a jar with a well-fitting perforated lid. One animal is then taken in the left hand and held firmly by its pelvis, the hind legs being kept extended by hooking the fourth and fifth fingers over the animal's thighs. The thumb then gently wrinkles the skin on the back, and a size 18 needle is passed into a fold in the dorsolumbar region, care being taken not to penetrate the deeper tissues. The injection is

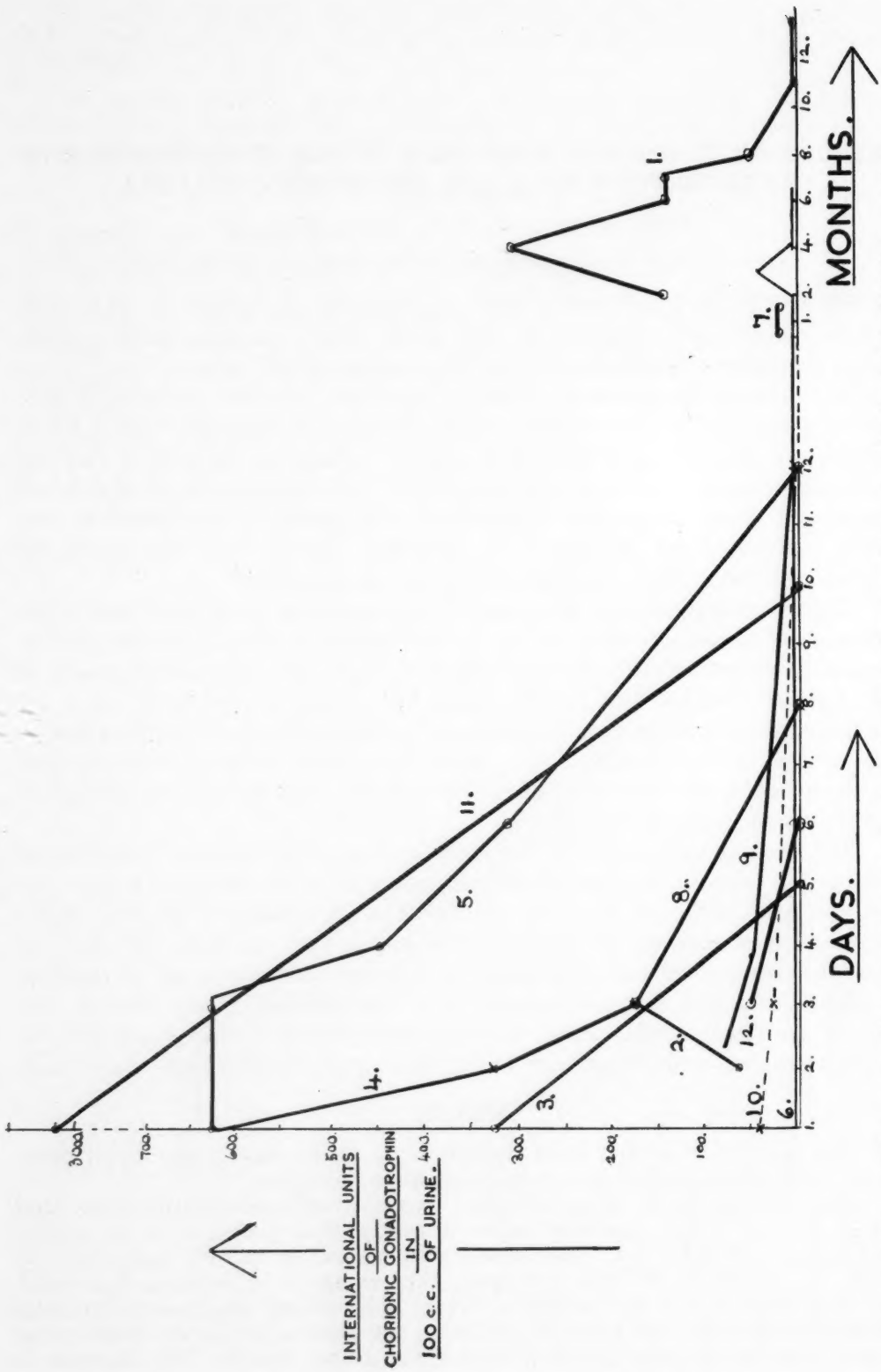


Fig. 1.—Titer of chorionic gonadotrophin in the urine of twelve patients after abortion of hydatidiform mole.

then made slowly. Half an hour later the animals are catheterized by inserting the tip of a smooth glass pipette into the cloaca. The animals should be held in a vertical position during this procedure so that the flow of urine is aided by gravity. A few drops of this urine is then examined on a glass slide under low power and with the light well cut down. If the test is positive, a few or many sperm will be seen. These can readily be differentiated from other cells and animalcules which may be present by their slender, curved shape, terminal flagellum, and by their progression, which is by gentle rocking movements.

The urine specimens were detoxified and concentrated by Scott's method.

Serum tests were carried out as I described in a previous communication. It is regretted that these tests have been done only in those patients investigated during the last 9 or 10 months, as previously toxic effects of serum and plasma upon the test animals made them unreliable. The difficulty has now been overcome. Tissue extracts have been prepared simply by washing the tissues in normal saline, gently blotting to remove as much fluid as possible, grinding in small glass tissue grinders with distilled water, and finally centrifuging, the supernatant fluid being used for injection. The titer of chorionic gonadotrophin quoted in each test (in urine, serum, and tissue) is the least amount of hormone that can be present. The actual amount lies between the amount quoted and double the quoted figure minus 4, 8, or 16, etc.

Example.—

If 50 ml. of urine, extracted and divided between two animals, gives a positive test, and 25 ml. treated in a similar way is found to be negative, and if the sensitivity of the animals (English) is 8 international units, then the least amount of hormone present must be

$$\frac{8 \times 100}{25} = 32$$ international units per cent. But 50 ml. may contain 15 international units and yet give the same results in the toads; therefore the hormone content may be as much as

$$\frac{15 \times 100}{25} = 60$$ international units per cent.

Similarly if a 25 ml. extract of urine is positive and a 10 ml. extract is negative the hormone content is between 64 and 120 international units per cent.

Fourteen patients with hydatidiform mole (Group I) and 7 patients with chorionepithelioma (Group II) were investigated.

Group I. Patients With Hydatidiform Mole.—

The age of the patients with hydatidiform mole ranged from 19 to 40 years, 9 being less than 30.

Two patients in this group developed chorionepithelioma and, of these, one aged 25 years is alive and well at the time of writing, and the other, aged 37 years, has died.

The range of titer of chorionic gonadotrophin in the urine in the postabortive period was 32 to 6,400 international units per cent (see Fig. 1) and in one patient in whom it was possible to investigate in the preabortive period, the titer was 1,600 to 3,200 international units per cent (see Fig. 2). The titer of chorionic gonadotrophin in mole tissue was variable. Intact moles were found to contain from 235 to 4,324 international units per gram, the smallest and the largest weight of tissue necessary to give a positive test being 0.00185 grams in Case 2, and 0.94 grams in Case 3. In pricked mole tissue both the titer and the range were low, and lay between 47 and 78 international units per gram. In contrast the titer in the vesicular fluid was high, and in this series it lay between 8,000 and 64,000 international units per cent.

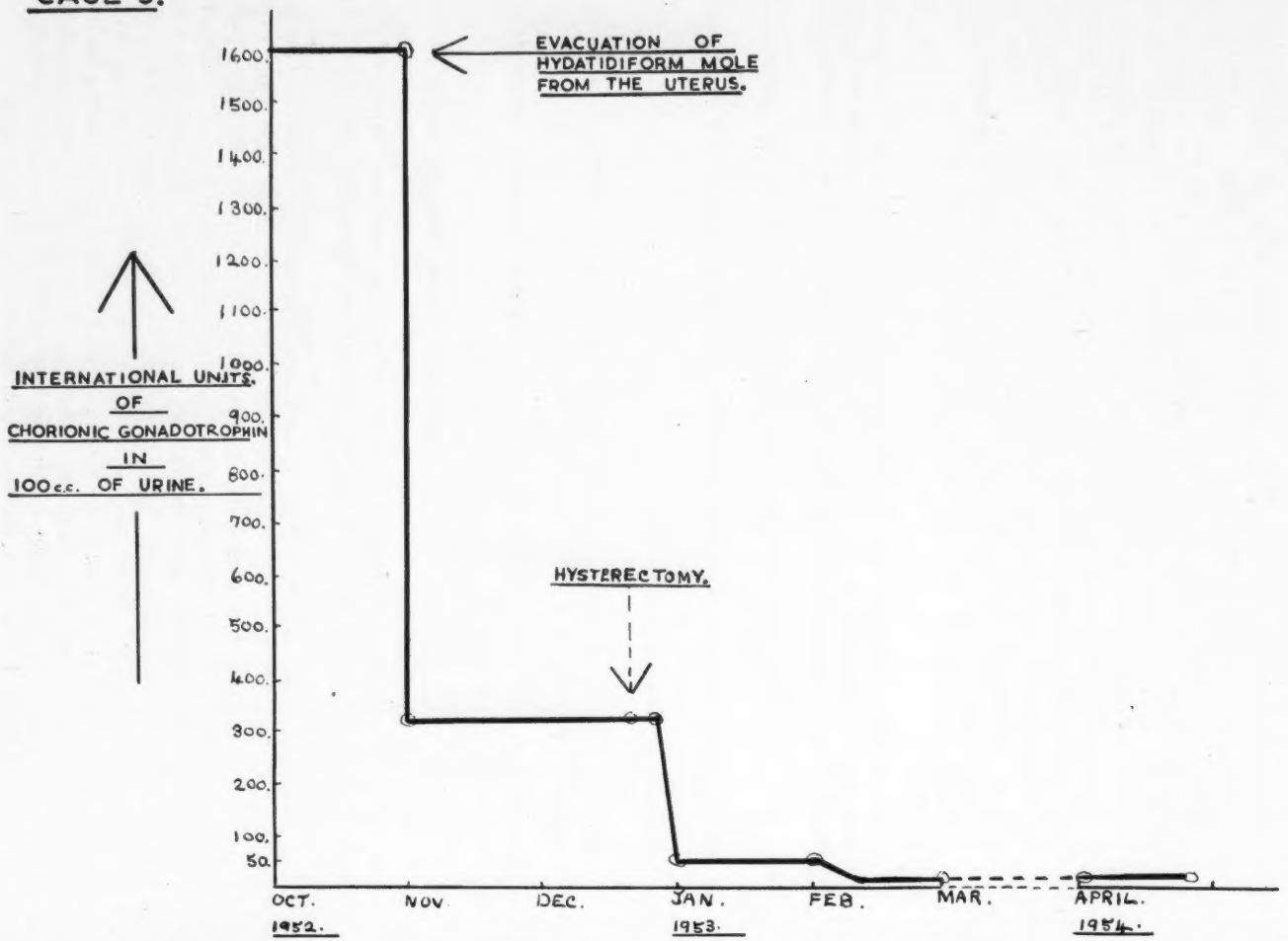


Fig. 2.—Titer of chorionic gonadotrophin in the urine of a patient recovering from a chorionepithelioma.

The length of time before negative urine tests were finally established in patients who did not develop a chorionepithelioma was from four days to eleven months, 9 patients having established negative tests within twelve days (Fig. 1).

The thirteenth and fourteenth patients, although both had hydatidiform mole, are included in the next group, since they both developed chorionepithelioma.

Group II. Patients With Chorionepithelioma.—

The age of the patients with chorionepithelioma was between 23 and 48 years, 4 being less than 25 years old. Two patients aged 23 years and one aged 37 years died.

Chorionepithelioma was preceded by a full-term normal delivery in 3 patients, by hydatidiform mole in 3 patients, and by abortion of nontypical hydatidiform tissue in one patient. The latent period before the first sign or symptom occurred was 3 to 6 months. In one case the tumor was removed before any sign or symptom occurred. The presenting sign or symptom was acute blood loss in 2 patients (one intraperitoneal and one hemoptysis), chronic blood loss per vaginam in 3 patients, morning nausea and vomiting in one patient, and, as already indicated, one patient had no sign or symptom but chorionic gonadotrophin was present in the urine.

The length of time before negative urine tests were established in this second group of patients was four days to ten months. The range of titer of chorionic gonadotrophin in the urine pre- and postoperatively in patients who survived was 32 to 64 and 32 to 640 international units per cent, respectively, and in the patients who died 32 to 1,066 and 1,600 to 6,400 international units per cent, respectively.

The range of titer of chorionic gonadotrophin in the extracts of primary growth was 27 to 2,600 international units per gram, the largest and the smallest amounts of tissue necessary to give positive tests being 0.34 and 0.006 gram, respectively. (Case 4 is discounted since the full range of tests was not possible due to shortage of test animals.)

The titer in the secondary tumor tissue was 100 to 200 international units per gram in Case 6, and 0.19 to 0.66 gram was found to be inert in Case 7.

The cerebrospinal fluid was investigated in Cases 6 and 7 only. Case 6 had 32,000 to 64,000 international units per cent, and negative test results were obtained with as much as 3 c.c. in Case 7.

The follow-up period in patients who are alive and well was twelve to thirty-five months.

Comment on Group I.—

The length of time in which positive tests for chorionic gonadotrophin were found in the urine of the patients in this group was variable. Nine patients had uninterruptedly negative tests within twelve days, and the rest took longer (Fig. 1). The prognostic significance of such findings is controversial. Park and Lees in their general review suggest that a complication has occurred if tests remain positive for longer than a month. Crew says that tests may remain positive for six months and yet not be associated with a chorionepithelioma. In the present series one patient had occasional positive tests for four months, and another (in whom the titer of hormone in the urine rose from 160 to 320 international units per cent, and who had an episode of uterine bleeding in the third month) had uninterruptedly postive tests for ten months (Cases 6 and 1, respectively), and neither developed a chorionepithelioma. It will be seen in Fig. 1 that the titer of chorionic gonadotrophin in the urine of both these patients was either low or only moderately high and not maintained. Many workers think that the occurrence of a complica-

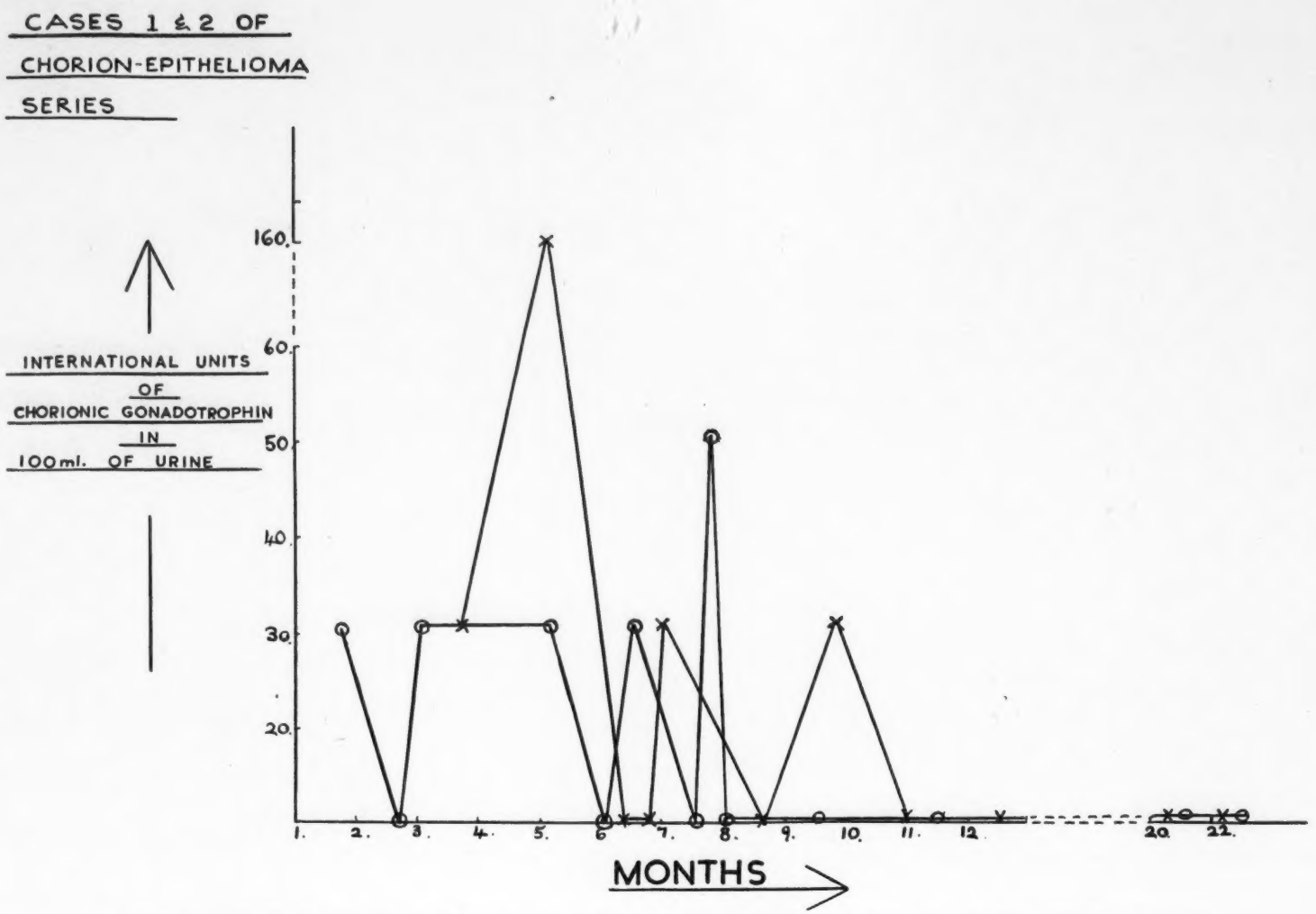


Fig. 3.—Titer of chorionic gonadotrophin in the urine of two patients after the removal of a chorionepithelioma.

tion is unlikely provided that the titer does not rise, and do not suggest that the actual amount of hormone is important. In this series a high, or a very high titer (more than 500 international units per cent) immediately after abortion was of little importance. Similarly a low titer (320 international units per cent or less) even if maintained for several months was associated with a good prognosis. A moderately high and maintained titer of hormone, however, was significant. For example, in the fifth patient (Fig. 2) the level of chorionic gonadotrophin, after a preliminary drop following the removal of the mole, remained constant but moderately high (320 to 640 international units per cent) for four weeks, during which time the uterus contained a chorionepithelioma, which at the time of removal measured 2 inches in diameter. The sixth patient also had a maintained and moderately high titer (320 to 500 international units per cent, Fig. 4), and by the time a hysterectomy was performed, six months after abortion, metastases had already occurred. In this series, therefore, the titer of hormone in the urine after the immediate postabortive period (that is after the twelfth day) was of greater diagnostic and prognostic significance than the time interval in which positive tests occurred.

Extracts of Mole Tissue.—

A few points occurred in these investigations which may be useful in the interpretation of future results. In the third patient, for example, although the mole tissue appeared, both to the naked eye and on microscopic examination, to be identical with the mole tissue in the second patient, it was found necessary to use 400 times the weight of that used in the second patient in order to obtain a positive test.

In the fifth patient (a twin pregnancy) the hydatidiform mole tissue contained weight for weight nearly ten times as much chorionic gonadotrophin as did the placenta, this difference being due to the high hormone content of the vesicular fluid.

An extract made from 4.5 grams of retained products in the tenth patient (one month after abortion of a mole) was found to be inert, whereas the original tissue had contained at least 16 to 32 international units per gram, and may have contained more, the full range of tests not being possible due to a shortage of animals.

The serum and relatively large amounts of pricked mole in the twelfth patient gave negative tests, whereas the extract of the intact mole contained 59 to 118 international units per gram of chorionic gonadotrophin, and the vesicular fluid 8,000 international units per cent. This was doubtless due to the presence of a large amount of fibrin clot, which would make it unlikely that the mole tissue was in close contact with the maternal circulation.

In spite of the wide range of titer found in these investigations, it is probable that helpful information would be obtained if the chorionic gonadotrophin content were estimated in all tissues such as retained products, tumor fragments, and curettings following hydatidiform mole, since these may appear normal, and yet (as occurred in the second, fourth, and sixth patients in Group II), the uterus contain a chorionepithelioma. Assay of the urine as well for this hormone should not of course be omitted.

Comment on Group II.—

The prolonged period of time in which positive tests of low titer can occur in the urine and yet not be associated with secondary spread is shown in Fig. 3 (Cases 1 and 2). It will be seen that uninterruptedly negative tests were not obtained for ten and seven months, respectively, and that the fluctuation of the level of hormone was on the whole slight. Follow-up examination of these patients shows that they are well thirty-five and twelve

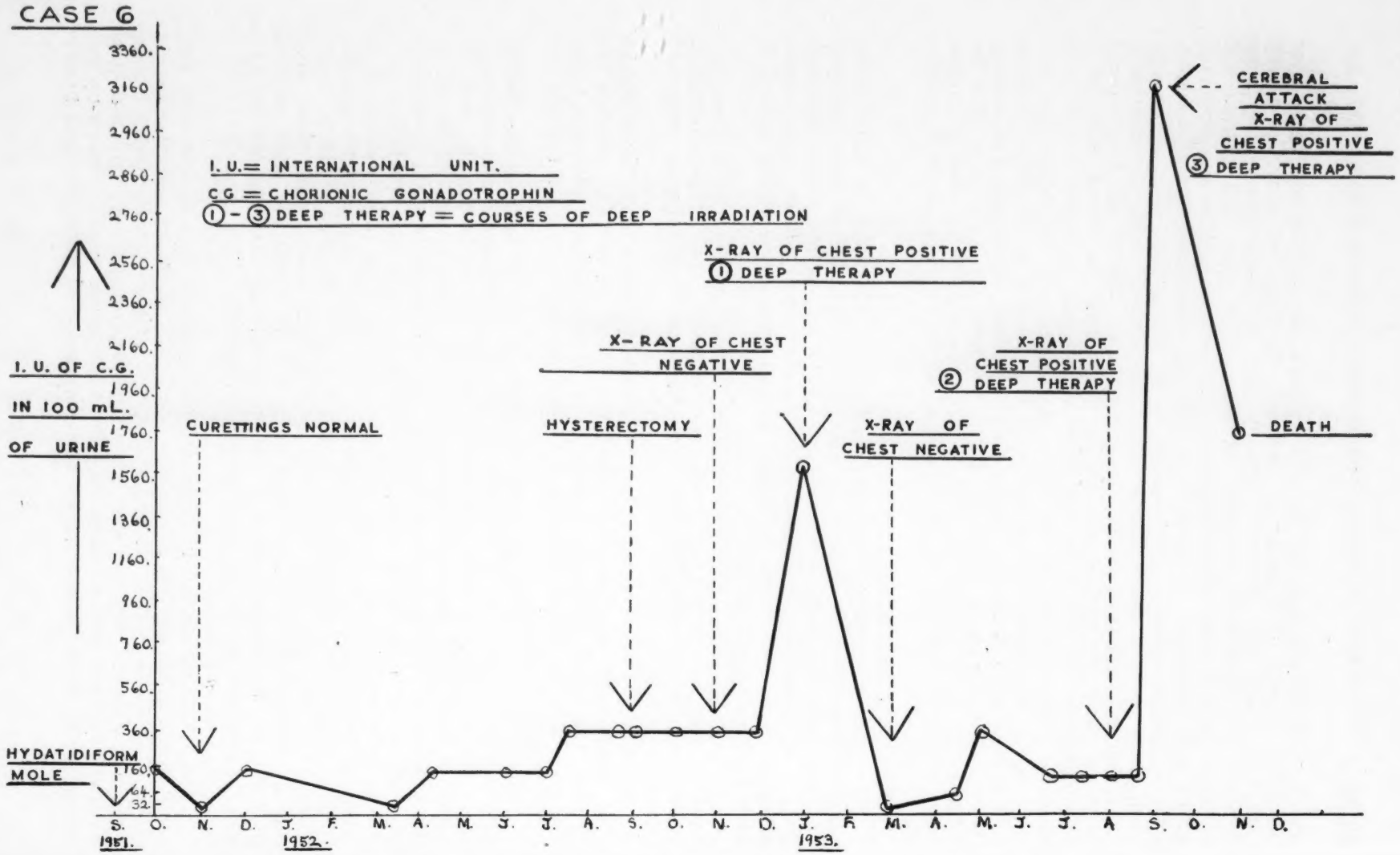


Fig. 4.—Titer of chorionic gonadotrophin in the urine of a patient dying from chorionepithelioma.

months later. In retrospect, it seems, therefore, that, as in the patients with hydatidiform mole, the low titer of chorionic gonadotrophin was more important in prognosis than either the length of time during which it was present in the urine, or the small fluctuation in its level.

The urine test results in the third patient (preoperatively 32, and postoperatively 64 international units per cent) are noteworthy inasmuch as they are an example of the low titer of chorionic gonadotrophin which may be found in some cases of chorionepithelioma.

From the laboratory point of view the sixth patient presented many difficulties. A record of investigations and treatment during the course of this patient's illness is depicted in Fig. 4. It will be seen that the titer of chorionic gonadotrophin did not fall after hysterectomy (a finding which is probably always associated with the presence of widespread metastases), but that there was a substantial fall with each course of deep therapy. This finding has also been noted by Payne, who records that tests may even become negative for a short time following this form of therapy. Assay of the tumor tissue in this patient showed that the primary growth contained 1,333 international units per gram, and as little as 0.006 grams gave a positive test. The titer in the secondary tumors in the kidneys and in the lungs was one-tenth and one-third of the amount in the primary tumor, respectively. Zondek (1942) records one-eighth in the specimens investigated by him.

As in the hydatidiform mole series, no correlation could be found between the appearance (both gross and microscopic) of the tumor tissues and their content of chorionic gonadotrophin.

The chorionic gonadotrophin content of this patient's serum shortly before death was 48,000 to 96,000 international units per cent, and in a postmortem specimen of cerebrospinal fluid it was 32,000 to 64,000 international units per cent, both results being in marked contrast to those found in similar investigations in the next patient (Case 7).

Test results in the seventh patient are remarkable. The urine contained 1,600 to 3,200 international units per cent, whereas relatively large amounts of tumor tissue, serum, and cerebrospinal fluid were found to be inert. The patient was not receiving drugs at the time the blood specimens were taken, and the animals did not show any signs of depression or illness either during or after injection. Searching the literature, I have been unable to find a case recorded in which the serum and the urine test or urine and tissue test results were conflicting. Many cases of chorionepithelioma and a few of hydatidiform mole as well as a few of normal pregnancy are recorded in which there have been negative tests throughout the whole of the illness or gestational period, but in these patients either the urine only or the serum only seems to have been investigated.

Fig. 4.—Titer of chorionic gonadotrophin in the urine of a patient dying from chorionepithelioma.

General Comment

The laboratory diagnosis of hydatidiform mole and chorionepithelioma from the titer of chorionic gonadotrophin in either the urine or the serum has always been difficult. Any single titer found in both the pre- and postabortive phases of a hydatidiform mole and in the pre- and postoperative phases of chorionepithelioma can be, and frequently is, found also at some phase of normal pregnancy. In most pregnancies the titer of chorionic gonadotrophin, unlike the titer of this hormone in hydatidiform mole and chorionepithelioma, follows a well-recognized curve, the peak occurring between the sixtieth and seventieth days and usually lasting for six to ten days. As suggested by

Zondek, Crew, and others, a series of quantitative tests for just longer than this period should at once differentiate between a normal and a pathological pregnancy. To a large extent this is true. Indeed, this method was adopted with success in Cases 1 and 6 in the hydatidiform mole series, and in Case 6 in the chorionepithelioma series, but it should be pointed out that this method is not always applicable, and may offer practical difficulties. The peak period, although usually lasting from six to ten days, does not invariably do so. An extended peak period may occur with twins in which one placenta is normal and one a hydatidiform mole, it may also occur in normal twin pregnancy, and indeed it is not uncommon in a normal single pregnancy, especially when associated with hyperemesis and other toxic signs.

The laboratory diagnosis of the presence of a chorionepithelioma following a full-term normal delivery, or following abortion, and the differentiation of this from retained products are financial or economic rather than laboratory problems. It is contended that all patients should have the urine tested for chorionic gonadotrophin as a routine after delivery, and, if delivered in hospital, before being discharged, to prevent defaulting. It may be objected that the condition is rare, that the work involved would be too great, the staff employed too large, and the cost too much. But is this condition so rare? And is the cost too much? The 7 cases in this series occurred in three years within a radius of 34 miles. Now, four months later, 2 further cases, both following full-term normal deliveries and both ending fatally, have occurred in the same area.

The cost of pregnancy tests in this series has been between 6d. and 9d. each, and it is estimated that the fifth case cost approximately £50 to detect. The cost today, however, is probably much less, due to keeping the test animals when not in use in a state of hibernation (Allison) and by using one animal for each test instead of two. It should be remembered that blood grouping and Wassermann reactions have been done on all pregnant patients, and many of them have had a hemoglobin estimation, so that a urine test as well for chorionic gonadotrophin is perhaps not so excessive as it would at first seem. In the days when a pregnancy test took anything from two to four days to do, the proposition might well have been considered to have its difficulties. Now the situation is different. Today 75 per cent of all pregnancy tests can be done in thirty minutes or less, and 95 per cent within two hours (Allison) and since almost every country in the world can supply frogs and toads suitable for this assay, it now seems reasonable to review this situation. By routine testing it would be practicable to detect cases such as those recorded in this series of chorionepithelioma (Cases 4 and 7) so early (at the seventh or eighth postpartum day, for example) that operative intervention can be undertaken at a time when a successful result can be expected. Further, if careful investigation were undertaken of each case as it was detected, both from an endocrinological and a pathological point of view, light might be shed not only upon the etiology of this condition, but its control and cure by medical means might become possible.

Summary

The titer of chorionic gonadotrophin in the urine, and in abnormal tissues when these have been available, is recorded in:

Fourteen patients with hydatidiform mole, investigated in the postabortive period.

One patient with hydatidiform mole, investigated in the pre- and postabortive periods.

Four patients with chorionepithelioma, investigated both in the pre- and in the postoperative periods.

Two patients with chorionepithelioma investigated in the postoperative period only.

The length of time before negative urine tests for chorionic gonadotrophin were established was from four days to ten months.

Seventy-five per cent of the patients with hydatidiform mole had negative urine tests within twelve days.

The follow-up period in the hydatidiform mole series was two weeks to thirty-three months and in the chorionepithelioma series twelve to thirty-five months.

The interpretation and significance of the titer of chorionic gonadotrophin in the urine in hydatidiform mole and in chorionepithelioma are discussed. It is thought that the actual level of the hormone in the urine as well as the variation in level is of more significance than the time interval in which positive tests occur. It is suggested that, since the toad and frog test is simple, accurate, and rapid, it is now practical for all patients to have a urine "all-clear" test for chorionic gonadotrophin following a full-term normal delivery and after abortion, so that cases of chorionepithelioma can be detected so early that operative intervention may be undertaken at a time when a successful result can be expected.

References

Aëtius XVI: Geburtshulfe und Gynäkologie Bei Aetios von Amida. Ed. Wegscheider, Berlin, 1901.
Allison, R. M.: Surg., Gynec. & Obst. **98**: 446, 1954.
Allison, R. M.: J. Endocrinol. **11**: 377, 1954.
Aschheim, S., and Zondek, B.: Klin. Wchnschr. **7**: 8, 1928.
Crew, F. A. E.: Brit. M. J. **1**: 993, 1936.
Frank, R. T.: J. Mt. Sinai Hosp. **10**: 112, 1943.
Marchand, F.: Monatsschr. Geburtsh. u. Gynäk. **1**: 419, 1895.
Novak, E., and Koff, A. K.: Am. J. Obst. & Gynec. **20**: 161, 1930.
Park, W. W., and Lees, J. C.: Arch. Path. **49**: 73, 1950.
Payne, F. L.: Surg., Gynec. & Obst. **73**: 86, 1941.
Sänger, M.: Centralbl. Gynäk. **122**: 33, 1889.
Scott, L. D.: Brit. J. Exper. Path. **21**: 320, 1940.
Seigler, S. L., Ravid, J. M., and Tobin, S. M.: Am. J. Obst. & Gynec. **60**: 586, 1950.
Zondek, B.: J. A. M. A. **108**: 607, 1937.
Zondek, B.: Am. J. Obst. & Gynec. **49**: 397, 1942.

THE ECTOPIC CHORIOCARCINOMA*

F. F. JORDAN, M.D., F.A.C.S., CLEVELAND, OHIO

(From the Division of Obstetrics and Gynecology, St. Luke's Hospital)

CHORIOCARCINOMA or chorionepithelioma is a very malignant pelvic tumor. This neoplasm nearly always develops during the reproductive period. A few cases have been reported in children, however, and some after the menopause. The oldest patient reported was 71 years old. Although it is usually associated with pregnancy, it may develop in the male. The tumor may arise from the testicle, from the ovary, or from the mediastinum.

The following have been given as its most probable origin: (1) teratomas and (2) the chorionic ectoderm. In the latter case the tumor is of fetal rather than of maternal origin.

It has been estimated that 50 per cent of the cases follow hydatidiform mole; 25 per cent follow abortion; and 25 per cent term pregnancy.

The choriocarcinoma generally arises from a tissue which normally has physiological characteristics usually associated with a malignancy. The trophoblastic tissue is destructive; it penetrates the decidua and often the muscularis; and it has physiological metastases. It produces the chorio-gonadotrophic hormone.

Just when the unknown factor which governs the growth of the chorionic epithelium fails to function properly is not definitely known. Douglas[2] reported a case in a woman who was five months pregnant, with a living child, and who had metastatic lesions of a chorionepithelioma in the vagina and lungs, with the primary lesion in the vagina.

From the physiological to the most pathological states in the growth of the chorionic ectoderm, one finds chiefly quantitative variations from its normal characteristics. This accounts for the different classifications as: (1) hydatidiform mole (benign and malignant); (2) syncytial endometritis; (3) chorioadenoma destruens; (4) choriocarcinoma.

Symptoms.—

The tumor, when found in the ovaries of a child, often produces precocious puberty. There is generally severe anemia. Infection is common. Other signs and symptoms are hemorrhage, pain, etc., depending on the location of the tumor, as in the uterus, vagina, abdomen, chest, or brain.

Location.—

The primary tumor is generally found within the uterus. A few cases have been reported with the origin in the tubes. In rare cases, the reproductive organs are free of tumor, the lesion being found in other viscera. This condition is referred to as an extragenital or ectopic choriocarcinoma. Less than 30 such

*Presented at a joint meeting of the Pittsburgh and Cleveland Obstetrical and Gynecological Societies, Cleveland, Ohio, March 22, 1954.

cases have been reported to date. Various authors suggest the following possibilities as to the origin of the extragenital tumors:

1. Metastatic lesions, the primary focus having regressed or been expelled. This might be possible if the lesion in the placenta was completely cast off and no uterine growth remained. An unknown factor normally controlling chorionic growth might have caused regression. Novak and Koff[5] reported a chorion-epithelioma removed from the brain in November, 1928. Review of the curettings of the previous July showed the same tumor. At autopsy no sign of the tumor was found in the uterus.

2. Trophoblastic emboli which have become malignant. The phenomenon of deportation of trophoblasts found in the blood stream, often lodging in the lungs, was described by Schmorl.[19]

3. Teratomatous growth with the survival of only the chorionepithelioma-tous part. This could well account for the cases found in children.

Metastasis.—

Metastasis is generally by way of the blood stream, the veins being the chief route. They are found in the following frequency: lungs (75 per cent), vagina (50 per cent), liver, intestines, kidneys, and the brain. The lesions are generally dark or hemorrhagic and are often mistaken for hematomas. They may be bright red brown or red,'' the less degeneration, the more brilliant the color. The cut surface is often necrotic and hemorrhagic.

Diagnosis.—

Lesions in tissues to which metastases of this tumor are common should always suggest the possibility of choriocarcinoma, especially with the history of a recent pregnancy. Amenorrhea is frequent. X-ray of the lungs is very important. Probably the most reliable information is obtained from the pregnancy test. This test should be negative two weeks after the termination of a normal pregnancy, and in three or four months after a molar pregnancy.

Negative reactions should be repeated and a constant or rising titer makes the diagnosis more certain. Zondek stresses the Aschheim-Zondek test on the spinal fluid. A new pregnancy must not be overlooked. A dilatation and curettage is of value in the differential diagnosis, but is seldom conclusive. The lesion may be missed because it may lie deep within the uterine wall or in other organs. A well-formed decidua is often present. Biopsy of accessible lesions is a very reliable procedure. Cystoma of the ovaries is present in one-third of the cases.

The lesions usually progress rapidly with signs of infection, necrosis, and hemorrhage.

Prophylactic Treatment.—

The placenta should be inspected in all cases. Even a small area showing signs of hydatidiform degeneration is significant. Hysterectomy is probably wise in the case of a large mole when sacrifice of the uterus would be no great loss. When the diagnosis of a mole is made, the uterus should be completely emptied. The vaginal route is generally the wiser method. Rarely can the curettings be relied upon for a definite diagnosis. The pregnancy test, though

not infallible, is very valuable. The test should be made every two weeks the first three months, at least once every month the next year, and every three months the following year. Clinical symptoms should not be disregarded. When the test is positive, quantitative titrations should be done. A constant or increasing titer is alarming.

Treatment of Choriocarcinoma.—

When possible, the lesion should be removed surgically. X-ray therapy is generally used, although the results are questionable. Antibiotics are indicated for the infection. Blood transfusions are required frequently. Quantitative hormone tests give some index as to the status of the lesion. Usually the patient's condition deteriorates rapidly. With modern medicine and surgery the outlook is not as gloomy as in Ewing's day.

The case reported by Howard Taylor, Jr.,[8] of New York is worth repeating: (1) Patient 32 years old. (2) Abortion in 1935. (3) Normal pregnancy in 1937. (4) Hydatid mole in 1939. (5) A-Z test negative until 1942. (6) Pulmonary lesion in 1942. (7) Lobectomy in 1943. Diagnosis: chorionepithelioma. (8) Hysterectomy and bilateral salpingectomy showed no chorionic lesion. (9) Patient had a negative A-Z test and was in good health three years later.

Dilworth's[1] reports with very thorough study and early surgery are encouraging.

Cases at St. Luke's Hospital.—

From 1937 to 1953, inclusive, at St. Luke's Hospital, there were 36,027 deliveries. There were admitted and treated during this time 26 patients with hydatidiform mole, an incidence of approximately 1 in 1,400 deliveries. Of these moles, only 2 were malignant. These patients had positive Friedman tests and had hysterectomies. Both recovered.

During this seventeen-year interval covering 36,027 deliveries, only one true choriocarcinoma developed in a term pregnancy, making an incidence of 1 in 36,000 deliveries. This was an extragenital choriocarcinoma.

CASE 1.—M. R., No. B12017, white, aged 37, gravida ii, para ii, had a term pregnancy in 1947, and a premature seven months' infant in September, 1949. There had been antepartum bleeding. The placenta was adherent and was removed manually. The pathological report of the placenta was "no pathological diagnosis."

The patient was admitted to the hospital six months post partum with a history of: (1) rusty sputum with cough for one month, (2) fever, (3) diarrhea, (4) vomiting, and (5) blurring of vision. The patient had always been a heavy smoker. For several years, râles could always be heard throughout the lungs. According to the family history, her father had had carcinoma. During the hospital stay there were many tarry stools.

The x-ray showed a pulmonary lesion with effusion. Cytological examinations gave no clue as to the specific diagnosis. There was a rapidly progressing anemia. Soft masses the size of tennis balls were palpable in the adnexa. By the Salmon-Geist-Salmon-Frank pregnancy test at Mt. Sinai Hospital, Cleveland, the spinal fluid was in a dilution of 1 to 500 and the urine positive in 1 to 10,000. Antibiotics were used. Frequent transfusions were necessary.

The pathological report at necropsy was the following: Choriocarcinoma in the following organs: (1) lungs, (2) diaphragmatic pleura, (3) spleen, (4) mediastinal lymph nodes, (5) liver, (6) kidneys, (7) brain, (8) mesenteric lymph nodes and (9) jejunum with perforation and intussusception (Figs. 1 to 6). There was a marked decidual reaction

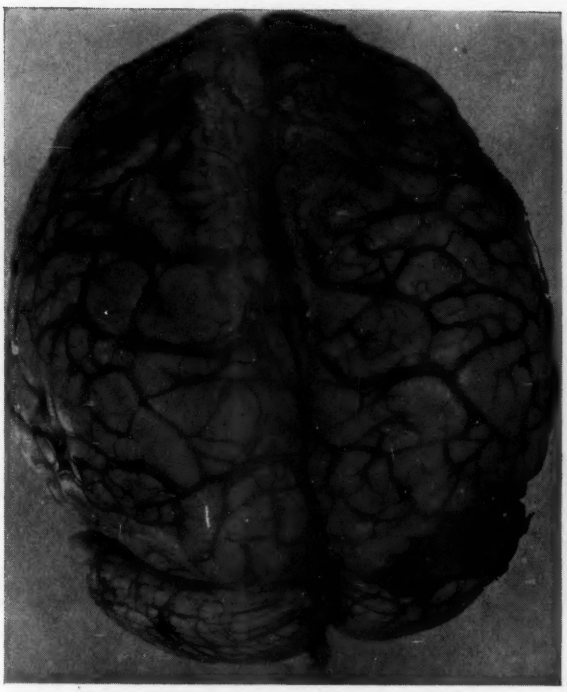


Fig. 1.—Chorionepithelioma in occipital area of brain.

Fig. 2.—Only the apex of lung is free from the tumor.

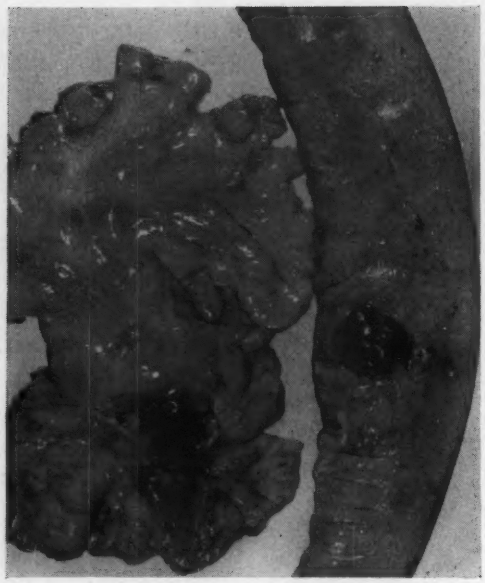


Fig. 3.

Fig. 4.

Fig. 3.—Jejunum showing area of tumor and perforation.
Fig. 4.—Large nodules in liver.

Fig. 5.—Syncytial cells and round-cell infiltration.

in the endometrium. Multiple lutein cysts were found in the ovaries which measured approximately 10 cm. each. Although multiple sections were made of the uterus and tubes, no sign of chorionepithelioma could be found.

During this interval, we had in this hospital two other patients who had been delivered and treated previously at other hospitals.

Fig. 6.—Multiple lutein cysts of both ovaries.

CASE 2.—M. W., No. 195084, 23 years old, gravida ii. Diagnosis: choriocarcinoma of lungs, vagina, and uterus following a late abortion.

CASE 3.—N. S., No. A5354, white, 23 years old. Diagnosis: choriocarcinoma of the uterus, lungs, and vagina following a term pregnancy.

These three patients had pulmonary metastases. They lived a very short time. It is very questionable if the x-ray therapy had any effect on the outcome.

Between the termination of the pregnancy and death, the shortest interval was 44 days. This period, in the case of ectopic chorionepithelioma, was 7 months. The mean interval (the period from delivery to death) reported by Park and Lees[17] in 60 cases of choriocarcinoma, diagnosed at autopsy or shortly before death, was 6.1 months.

Summary

1. Choriocarcinoma is a very malignant and rapidly fatal tumor.

2. Excessive vaginal bleeding, and lesions of the vagina, lungs, and liver, especially following a recent pregnancy, should suggest the possibility of a chorionepithelioma.

3. Most of the cases can be diagnosed by biopsy, x-ray, history, clinical findings, and hormonal pregnancy tests.

4. These methods of diagnosis should be used routinely, especially after the hydatidiform mole.

5. When the diagnosis is made early, and only a solitary lesion is present, surgery offers some hope in prolonging the patient's life.

6. If in the early stage the lesion is in a less malignant phase, early recognition and treatment may offer a better prognosis.

References

1. Dilworth, E. E., Mays, C. R., and Hornbuckle, L. A.: AM. J. OBST. & GYNEC. 60: 763, 1950.
2. Douglas, G. F., and Otts, O. M., Jr.: AM. J. OBST. & GYNEC. 57: 401, 1949.
3. Hertig, A. T., and Sheldon, W. H.: AM. J. OBST. & GYNEC. 53: 1, 1947.

4. Maun, M. E., and Green, W. M.: AM. J. OBST. & GYNEC. 46: 738, 1943.
5. Novak, Emil, and Koff, A. K.: AM. J. OBST. & GYNEC. 20: 153, 1930.
6. Rubin, I. C.: AM. J. OBST. & GYNEC. 41: 1063, 1941.
7. Nuckols, H. H., and Fine, Charles S.: AM. J. OBST. & GYNEC. 65: 990, 1953.
8. Maier, H. C., and Taylor, H. C., Jr.: AM. J. OBST. & GYNEC. 53: 674, 1947.
9. Freeth, D., and McCall, A. J.: J. Obst. & Gynaec. Brit. Emp. 57: 757, 1950.
10. Berman, Lawrence: Am. J. Cancer 38: 23, 1940.
11. Bell, E. T.: Text Book of Pathology, ed. 6, Philadelphia, 1947, Lea & Febiger, p. 403.
12. Hobbs, J. E., and Bortinck, R. R.: AM. J. OBST. & GYNEC. 40: 832, 1940.
13. Curtis, Arthur H.: A Textbook of Gynecology, ed. 4, Philadelphia, 1942, W. B. Saunders Company, pp. 322-338.
14. DeLee, J. B., and Greenhill, J. P.: The Principles and Practice of Obstetrics, ed. 8, Philadelphia, 1943, W. B. Saunders Company, p. 569.
15. Eastman, N. J.: Williams Obstetrics, ed. 10, New York, 1950, Appleton-Century-Crofts, Inc., p. 534.
16. Novak, Emil: Gynecological and Obstetrical Pathology, ed. 2, Philadelphia, 1947, W. B. Saunders Company, pp. 442-446 and 487-513.
17. Park, W. W., and Lees, J. C.: Arch. Path. 49: 73, 1950.
18. Payne, Franklin L.: Surg., Gynec. & Obst. 73: 86, 1941.
19. Schmorl: Centralbl. Gynäk. 8: 169, 1893.

10515 CARNEGIE AVENUE

EPIDERMOID CARCINOMA ARISING IN A BENIGN CYSTIC TERATOMA

A Report of 15 Cases

WILLIAM F. PETERSON, MAJOR, USAF(MC),* EDWARD C. PREVOST, M.D., FREDERICK T. EDMUNDS, M.D., J. MASON HUNDLEY, JR., M.D., AND FRANK K. MORRIS, M.D., BALTIMORE, MD.

(From the Departments of Gynecology of the University of Maryland School of Medicine and Hospital, and Lutheran Hospital of Maryland)

BENIGN cystic teratomas, a group comprising 11.1 per cent of all ovarian neoplasms according to our recent survey, like other benign tumors of the ovary, are liable to malignant degeneration. Somehow this fact has received little emphasis in the literature and by most standard textbooks. More attention seems to have been directed toward the etiology of this tumor, perhaps because of its appearance of a gross miscarriage of nature's art. This omission leads one to wonder how often a benign cystic teratoma is just discarded as an innocuous tumor or only one or two areas are taken indiscriminately for pathological examination.

Inasmuch as epidermoid carcinoma accounts for the great majority of cases of malignant degeneration occurring in benign cystic teratomas,[10] we wish to report this series of cases in an effort to try to formulate some clinical impressions on the course of this disease. If, in addition, interest is increased among our colleagues so that they too will be more aware of the malignant potentialities of these cysts, our efforts will be rewarded.

These case reports have been abbreviated because of a shortage of space and in the interest of the busy clinician. The microscopic reports have been eliminated in all but a few cases, inasmuch as the microscopic picture is given in the accompanying photomicrographs.

CASE 1.—Miss M. J., a 70-year-old nulligravida, was admitted to University Hospital on March 3, 1950, because of a mass in the lower abdomen noted on pelvic examination.

Laparotomy disclosed a large, free, cystic mass replacing the left ovary. The uterus was small and the right ovary atrophic. Examination of the peritoneal cavity, intestines, and other abdominal viscera failed to show any abnormalities. A total hysterectomy and bilateral salpingo-oophorectomy were performed.

Follow-up found the patient alive and well in December, 1953.

Pathology Report.—No. 68171. The specimen consisted of a cystic mass measuring 16 by 9 cm. On cut section it seemed to be multilocular, with a smooth, glistening wall. Throughout the cyst were indurated areas that appeared almost cartilagenous. A small amount of hair was present. The uterus, cervix, and tubes were grossly normal.

Impression.—Squamous-cell carcinoma arising in a dermoid cyst.

CASE 2.—S. R., a 31-year-old white woman, on examination after delivery was noted to have a mass in the pelvis.

*Presently stationed with the Department of Obstetrics and Gynecology, 1100th USAF Hospital, Bolling AFB, Washington 25, D. C.

Fig. 1.—Case 1. A spinal-cell form of epidermoid carcinoma is seen infiltrating the fibrous connective tissue stroma. Central necrosis is evident in several areas.

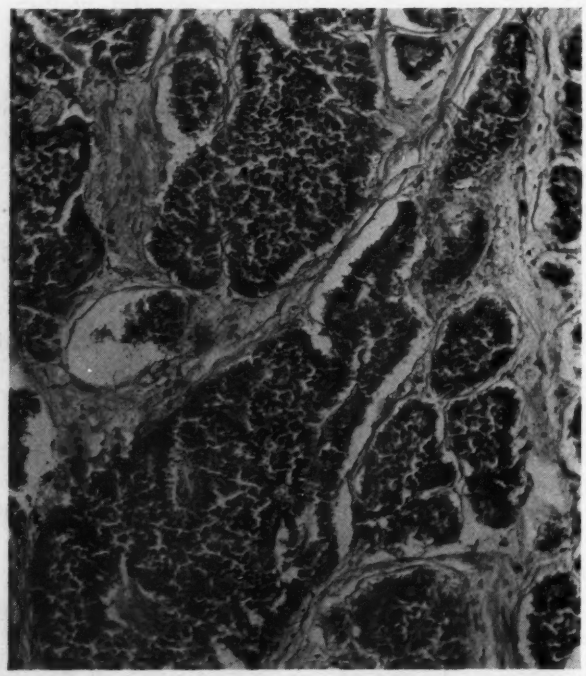


Fig. 2.—Case 2. Basal-cell carcinoma showing polyhedral cells lying in cords with peripheral palisading. An adenomatous pattern is evident with what appears to be glandular cells lining the lumina. (Courtesy Armed Forces Institute of Pathology.)

Laparotomy showed bilateral ovarian cysts, both of which were free. The remainder of the pelvis and abdomen was normal. A bilateral oophorectomy and appendectomy were performed.

Unfortunately no follow-up is available on this patient.

Pathology Report.—No. 266817 (Armed Forces Institute of Pathology). The specimen was an 8 by 7 by 3 cm. opened cystic structure filled with a greasy yellow-orange material and masses of hair. Within the cyst there were two solid areas which on section were composed of mixtures of partially cystic, gray, brown, and orange-yellow tissue. An 11 by 8 by 4 cm. similarily opened cyst contained a large quantity of hair and greasy material. Springing from the wall was a mass of orange-yellow tissue resembling fat, adjacent to which there was a 2 cm. nodule of firm, generally homogenous, pearly gray tissue. A small segment of apparently normal ovarian tissue was also recognized. A portion of the tube and appendix showed no gross lesion.

Impression.—Bilateral cystic teratomas of the ovaries with local basal-cell carcinoma.

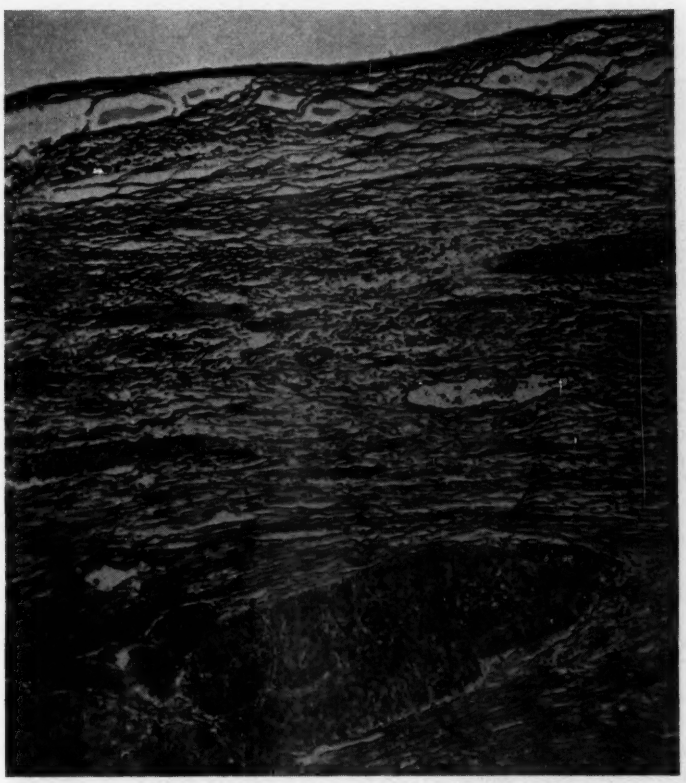


Fig. 3.—Case 3. The flattened stratified squamous epithelium lining the cyst wall is noted in the upper portion of the field. Nests of squamous carcinoma are seen invading the fibrous stroma.

Case 3.—F. H., a 68-year-old Negro woman, was admitted to Baltimore City Hospital in March, 1949, because of progressive abdominal enlargement, of two years' duration.

Laparotomy revealed many small uterine fibroids. The right tube was adherent to a large mass which was attached to the fundus of the uterus. The left tube and ovary were normal. One loop of ileum was slightly adherent to the posterior surface of the cystic mass. The abdominal viscera were found to be normal. A subtotal hysterectomy and bilateral salpingo-oophorectomy were performed.

Follow-up showed that the patient died of unrelated causes in six months. At this time she was free of apparent recurrence of the carcinoma.

Pathology Report.—No. 14668 (Baltimore City Hospital). The specimen consisted of a nodular uterus measuring 10 by 11 cm. The tubes and left ovary were normal. There was a large cystic mass that measured 20 by 14 by 15 cm., firmly attached to the uterus containing 1,000 c.c. of thick yellowish-greenish material. There was an area of 10 by 6 cm. which was white, nodular, and firm at the pole nearest the uterus. There were two masses that were soft, yellow, and covered with gray hair on the inner surface of the cyst in addition to numerous whitish granules. Section of the uterus showed many fibroids.

Impression.—Dermoid cyst with malignant change, right ovary, and fibromyomatous uterus.

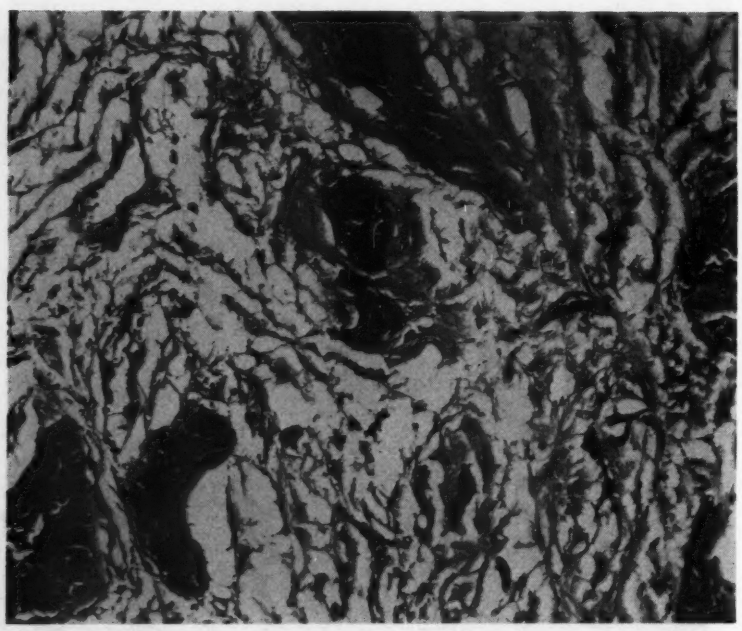


Fig. 4.—Case 4. A very anaplastic type of epidermoid carcinoma is seen invading a somewhat degenerated stroma. The carcinoma is of the transitional-cell variety.

CASE 4.—C. C., a 31-year-old Negro para i, was admitted to University Hospital in March, 1940, because of pain in the right lower quadrant of three months' duration.

Laparotomy showed the right ovary to be replaced by a large irregular cyst which was quite firm. Attached to this was the omentum and a large area of old granulation tissue around a gangrenous, perforated appendix. The uterus was the site of a small fibroid. The left tube and ovary appeared normal. A subtotal hysterectomy, right salpingo-oophorectomy, and appendectomy were performed.

Follow-up disclosed that the patient died in the fall of 1940, apparently of carcinoma.

Pathology Report.—No. 37928. The uterus was covered with coarse adhesions and except for a small fibroid appeared normal. The right tube was also covered with adhesions but was otherwise normal. The right ovary was replaced by a large mass covered with adhesions. The upper part was thicker than the lower which was more cystic. On section the lower pole showed a smooth wall filled with ceruminous material and hair. The upper pole showed a thick inflammatory wall with purulent, necrotic material. The appendix was 9 cm. long, covered with adhesions, and on section the wall was thickened and the lumen almost obliterated.

Microscopic examination showed one area in which there was definite continuity between the squamous-cell carcinoma and the squamous epithelium lining the cyst wall. In another area of the wall of the appendix there was a definite nodule of squamous-cell carcinoma.

Impression.—Benign cystic teratoma of the right ovary with squamous-cell carcinoma; metastatic squamous-cell carcinoma of the appendix; fibromyoma of the uterus.

CASE 5.—R. S., a 62-year-old white woman, was admitted to University Hospital in May, 1940, because of a pelvic tumor and bearing down pains of three months' duration.

Laparotomy disclosed that the right ovary was the site of a large simple cyst and the left ovary the site of a cyst which was adherent in the cul-de-sac and to the intestines. The cyst was ruptured during its removal and sebum, hair, and other material were freed in the pelvis. Subtotal hysterectomy and bilateral salpingo-oophorectomy were performed after frozen section had shown squamous-cell carcinoma in the dermoid cyst.

Follow-up revealed that the patient died in November of 1940 of metastatic carcinoma.

Pathology Report.—No. 38407. The uterus externally and on section appeared normal. The right ovary was replaced by a large, smooth, thin-walled cyst, 11 by 11 by 9 cm. with a smooth lining and containing clear fluid. The left ovary measured 10 by 12 by 10 cm., was partially cystic and partially solid, and was firmly adherent to the left tube. On section the cystic portion showed a yellow ceruminous material containing hair and a molar. The solid portion was whitish, firm and granular. The left tube was thick and granular.

Impression.—Simple serous cyst, ovary, right; dermoid cyst with squamous-cell carcinoma, ovary, left.

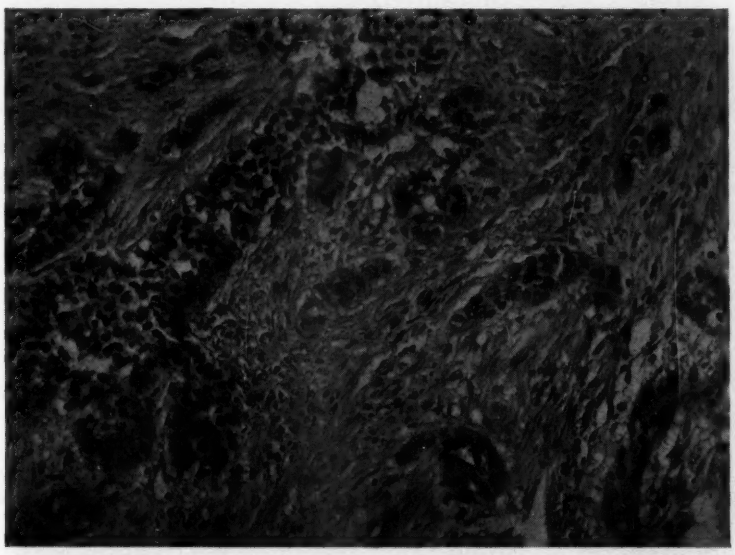


Fig. 5.—Case 5. Nests and cords of spinal-cell epidermoid carcinoma with evidence of an attempt at pearl formation.

CASE 6.—Miss B. D., a 57-year-old nulligravida, was admitted to University Hospital in June, 1937, because of lower abdominal soreness of eight weeks' duration and a tumor mass of two years' duration.

Laparotomy disclosed a large, thick-walled, very vascular cyst occupying the whole abdominal cavity and arising from the right ovary. The remainder of the abdomen was normal. Subtotal hysterectomy and bilateral salpingo-oophorectomy were performed.

Follow-up showed an uneventful course until her death in August, 1951, of cardiovascular disease.

Pathology Report.—No. 30525. The appendix, left tube, and ovary were normal and on section showed nothing unusual. The uterus was normal except for a small fibroid on the posterior wall. The right tube was thickened and elongated. The right ovary was replaced by a cyst, 18 cm. in diameter; the wall was smooth; however, it seemed thickened in several places and showed the growth of hair.

Impression.—Dermoid cyst of the right ovary with carcinomatous change; fibromyoma of the uterus.

Fig. 6.—Case 6. Spinal-cell epidermoid carcinoma is seen invading an area of thyroid tissue.

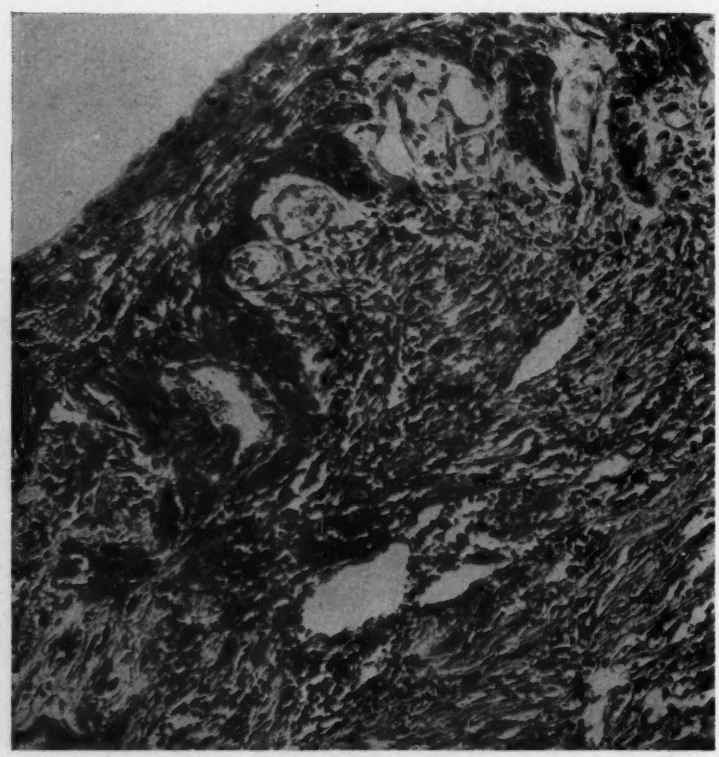


Fig. 7.—Case 7. The stratified squamous epithelium lining the cyst wall is noted to be hyperactive with a moderately anaplastic transitional-cell epidermoid carcinoma invading the stroma. Several small groups of malignant cells may be seen in the lower left portion of the field.

CASE 7.—(Courtesy of Dr. Edward H. Richardson, Baltimore, Maryland.) Miss E. B. M., a 46-year-old nullipara, was admitted to Union Memorial Hospital on June 12, 1937, because of a lump in the abdomen of three months' duration which had begun to enlarge more rapidly.

Laparotomy revealed a cystic tumor arising from the right ovary. This was delivered and found to be necrotic at several points. The left ovary was twice its normal size and quite irregular. At the right cornu the bladder peritoneum was adherent over a small necrotic area in the uterine wall. Subtotal hysterectomy and bilateral salpingo-oophorectomy were performed. (There were some anesthetic difficulties.)

Follow-up disclosed that the patient died of carcinomatosis in April, 1938, in spite of postoperative deep x-ray therapy.

Pathology Report.—The wall of the uterus was uniformly thickened and fibrous. Incorporated in the right broad ligament area was a large fungating mass the size of a lemon originating in the cornu of the right tube. The left ovary was the size of a hazelnut and contained several cysts. The right ovary was the size of a grapefruit and contained fatty substance and hair. The wall of the cyst was irregularily thickened at the site of its adhesions with the above fungating mass.

Impression.—Dermoid cyst of the right ovary with squamous-cell carcinoma; metastatic squamous-cell carcinoma of the broad ligament and cornu of the right tube.

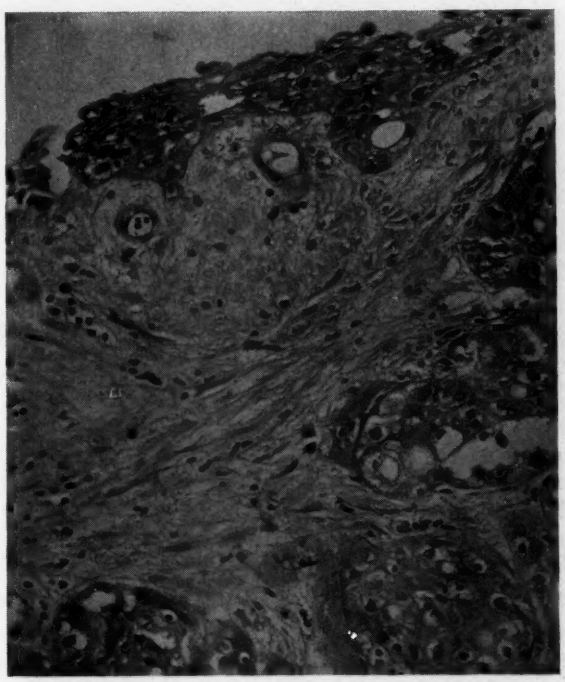


Fig. 8.—Case 8. A highly differentiated spinal-cell epidermoid carcinoma is noted infiltrating the stroma below the stratified squamous cell lining. Rather marked degenerative changes are seen in many of the malignant cells.

CASE 8.—(Courtesy of Dr. J. Miller and Dr. J. A. January, Hartford, Connecticut.) Mrs. G. B. G., a 51-year-old para i, was admitted to the Hartford Hospital on May 31, 1947, because of gradually increasing abdominal enlargement of two months' duration.

Laparotomy revealed a large cyst of the left ovary, evidently a dermoid, which was twisted clockwise one and one-half times. The sigmoid was attached at one pole and the omentum was also adherent. Total hysterectomy and bilateral salpingo-oophorectomy were performed.

Follow-up reveals that the patient was alive and well May 3, 1954.

Pathology Report.—(Ovarian Tumor Registry No. 316.) The uterus, tubes, and appendix were normal. The right ovary is 4 by 2 cm. in size and atrophic; however, it contained a 1 cm. cyst filled with a brownish, mucoid fluid. The left ovary was the site of a dermoid which in the collapsed form measured 16 cm. in diameter and contained hair and buttery material. The lining contained several small papillomatous structures measuring 2 to 3 cm. in diameter which had a finely cystic appearance. In some areas these had become confluent, forming plaques several centimeters in diameter. A rudimentary tooth was also present.

Impression.—Epidermoid carcinoma arising in a dermoid cyst of the left ovary; dermoid cyst of the right ovary.

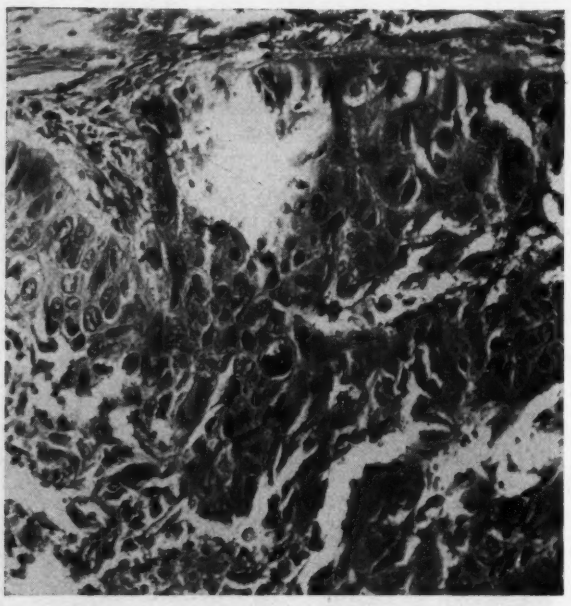


Fig. 9.—Case 9. An area of rather anaplastic spinal-cell epidermoid carcinoma. Mitotic figures are prominent.

CASE 9.—(Courtesy of Dr. Emery P. Page, Berkeley, California.) Mrs. M. M., a 57-year-old white woman, para ii, gravida ii, was admitted to the University of California Hospital because of increasing abdominal discomfort and progressive abdominal enlargement of six weeks' duration.

Laparotomy on March 24, 1948, showed 3,000 c.c. of ascitic fluid and a 15 cm. cystic mass arising from the right ovary. There had been rupture of the tumor at its upper portion with seeding of the peritoneum. A right salpingo-oophorectomy was performed.

Follow-up disclosed that the patient died of carcinomatosis eight months postoperatively.

Pathology Report.—(Ovarian Tumor Registry No. 455.) The specimen was a mass 16 by 9 by 7 cm. which on cut section was seen to be multicystic and contained soft, cellular, pale tissue. The cysts measured up to 3 cm. and were filled with clear fluid.

Microscopic examination showed that the cyst was lined by a well-developed stratified squamous epithelium. Distributed diffusely throughout the connective tissue stroma were seen many nests and cords of epidermoid carcinoma of the transitional-cell type.

Impression.—Dermoid cyst with epidermoid carcinoma, right ovary.

CASE 10.—(Courtesy of Dr. Richard Te Linde, John Hopkins Hospital, Baltimore, Maryland.) Mrs. A. B., a 78-year-old white nullipara, was admitted to Johns Hopkins Hospital April 19, 1947, because of progressive enlargement of the abdomen of seven years' duration. Six months prior to admission it began to enlarge more rapidly.

Laparotomy revealed a large, bulging, bluish, vascular, tense, cystic mass arising from the right adnexa. One solid area was suspicious. The remaining pelvic and abdominal viscera were normal. A subtotal hysterectomy and bilateral salpingo-oophorectomy were performed.

Follow-up disclosed that the patient was alive and well in February, 1954.

Pathology Report.—No. 70209. (Johns Hopkins Hospital.) The uterus, left tube, and ovary were essentially normal. The right tube was greatly elongated and atrophic and was stretched over the superior surface of a large ovarian dermoid cyst. The cyst was about 25 cm. in size, fairly thin-walled, and filled with a large amount of cheesy sebaceous material mixed with a large amount of hair. A relatively solid area at one pole was taken for section.

Impression.—Dermoid cyst of the right ovary with epidermoid carcinoma.

Fig. 10.—Case 10. Spinal-cell epidermoid carcinoma showing pearl formation. The cyst lining is evident in the upper portion of the field.

CASE 11.—(Courtesy of Dr. James R. Bloss, Huntington, West Virginia.) No clinical history is available as Dr. Bloss is deceased.

Laparotomy in December, 1946, revealed a large tumor arising from the right ovary. A subtotal hysterectomy and bilateral salpingo-oophorectomy were performed.

Follow-up showed that this patient was alive and well when last seen in January, 1947.

Pathology Report.—(Ovarian Tumor Registry No. 261.) The uterus contained many intramural and subserous fibroids but the endometrium was negative. The myometrium, beneath a fragment of the right tube, showed a rough and yellowish area the size of a quarter which on incision was friable and seemed to invade the myometrium. There was a large, cystic tumor, 26 by 21 cm., with a slightly knobby surface, the medial portion of whose wall was diffusely thickened over an area 8 cm. in diameter which corresponded to the ragged area on the myometrium. The cyst was filled with pultaceous material and a large amount of hair originating in a small projected area the size of a half dollar. Next to this was the previously described diffuse induration of the wall. On cut section this induration appeared yellowish, granular with intense yellow spots, and was very friable.

Impression.—Epidermoid carcinoma of a low degree of malignancy developing in the wall of a dermoid and extending to the myometrium; multiple myofibromas of the uterus.

CASE 12.—(Courtesy of Dr. Cary M. Dougherty, Louisiana State University School of Medicine, New Orleans, Louisiana.) Mrs. C. B., a 34-year-old Negro para iii, gravida iv, was admitted to Charity Hospital because of pain in the lower abdomen and urinary frequency of several months' duration.

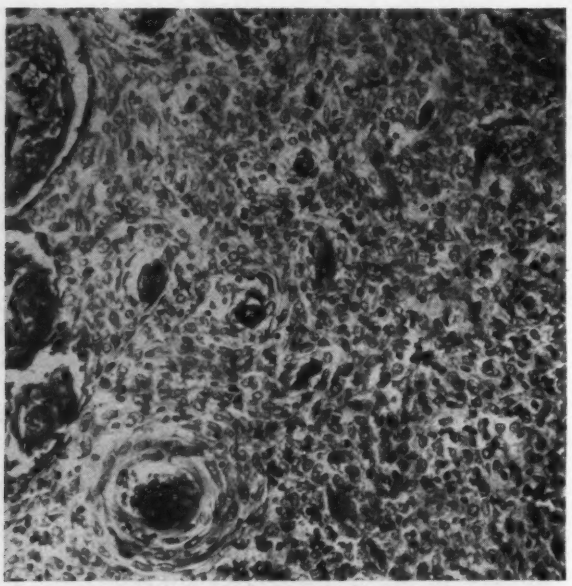


Fig. 11.—Case 11. Fields of solid carcinoma were noted in this case. The predominent cell type is spinal; however, the picture is clouded by the intense inflammatory reaction.

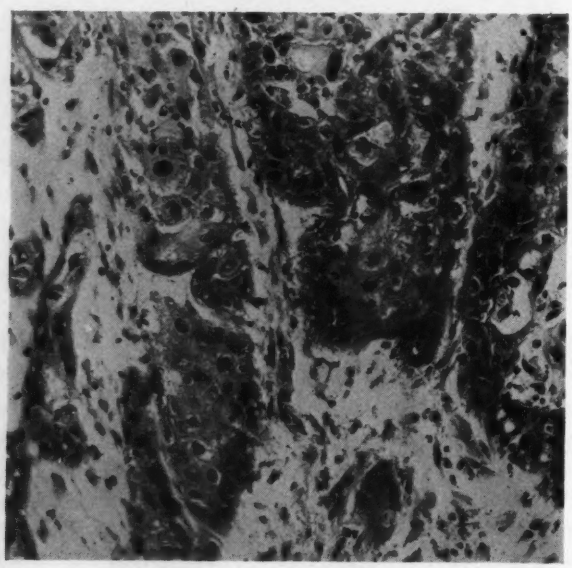


Fig. 12.—Case 12. Many well-differentiated spinal cells are seen intermingled with a more anaplastic, almost transitional-cell, form of epidermoid carcinoma. Pleomorphism and hyperchromatosis are marked.

Laparotomy showed that the uterus was twice normal size with several small, firm nodules embedded in it. A cystic mass the size of a large grapefruit occupied the right adnexa with the right tube plastered to the mass. The left adnexa were normal. A right salpingo-oophorectomy was performed.

Follow-up disclosed that the patient, who was pregnant, went uneventfully to term but, however, lost the baby after a difficult breech delivery in July, 1947. The patient then had a normal spontaneous delivery with a living child in 1950. She was last seen in August, 1954, at which time she was free of disease with an early pregnancy.

Pathology Report.—(Ovarian Tumor Registry No. 326.) The specimen consisted of a cystic mass and a portion of tube. The cyst was smooth and glistening, had a brownish-gray color, and measured 16 by 13 by 10 cm. The cyst was found to contain 100 c.c. of a yellow, cloudy fluid and a large amount of fat and a moderate amount of hair. The inner cyst wall was yellow and blackish in color.

Impression.—Dermoid cyst of the right ovary, with carcinomatous changes.

CASE 13.—(Courtesy of Dr. James A. Gough, Chicago, Illinois.) Mrs. R. B., a 38-year-old para i, was admitted to the hospital because of the acute onset of left lower abdominal pain.

Laparotomy in February, 1952, showed a large ovarian cyst which filled the pelvis and was adherent to the rectosigmoid. The cyst was inadvertently ruptured at this point with generous spill of a watery, dirty, yellow-gray fluid containing flocculent material resembling vernix caseosa. The right ovary, uterus, and the remainder of the pelvic cavity were normal. A total hysterectomy and bilateral salpingo-oopohrectomy were performed.

Follow-up revealed that the patient died of a recurrence of the malignancy in February, 1954.

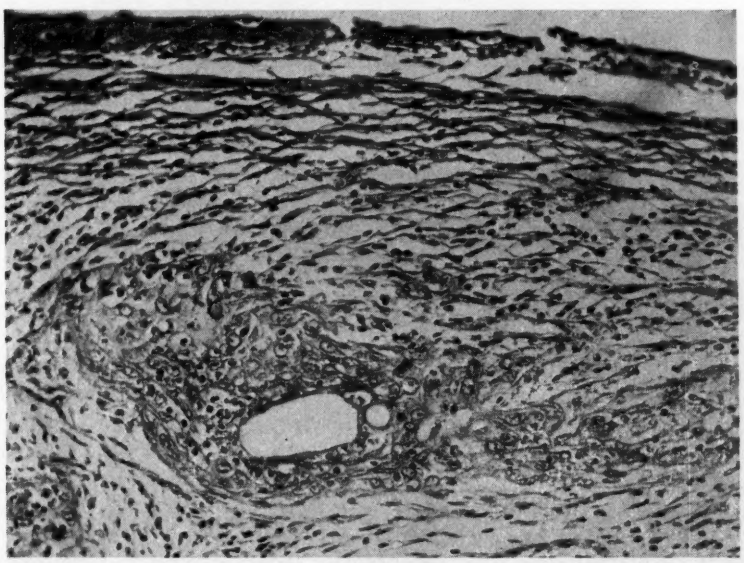


Fig. 13.—Case 13. An area of well-differentiated spinal-cell epidermoid carcinoma is seen lying in the stroma below the stratified squamous-cell lining. The lining is seen to taper down to almost one cell in thickness.

Pathology Report.—(Ovarian Tumor Registry No. 965.) The specimen was collapsed ovarian tissue measuring 11 by 7 by 4 cm. with a solid mass of tissue measuring 9 by 6 by 3 cm. protruding into the lumen and extending through the wall. This tissue was white with some yellowish mottling.

Impression.—Dermoid cyst with squamous-cell carcinoma of the left ovary.

CASE 14.—(Courtesy of Dr. L. A. Calkins, University of Kansas Medical Center, Kansas City, Kansas.) Mrs. M. C., a 42-year-old white woman, para ii, was admitted to Kansas University Hospital because of lower abdominal pain of two and one-half months' duration.

Laparotomy in October, 1944, showed a partially operable tumor mass, obviously an atypical carcinoma of the left ovary, the margins of which were transversed by loops of small intestine. The uterus, tubes, and right ovary were normal. About 95 per cent of the tumor mass was removed.

Follow-up showed that the patient went into shock and died 96 hours postoperatively.

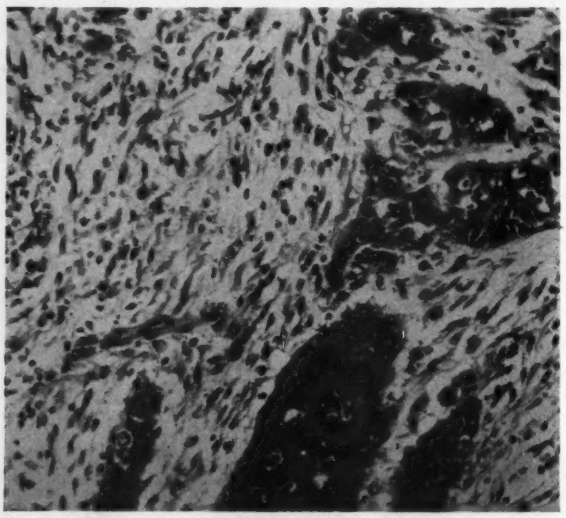


Fig. 14.—Case 14. Although of the spinal-cell variety the epidermoid carcinoma is marked by its pleomorphism and hyperchromaticity.

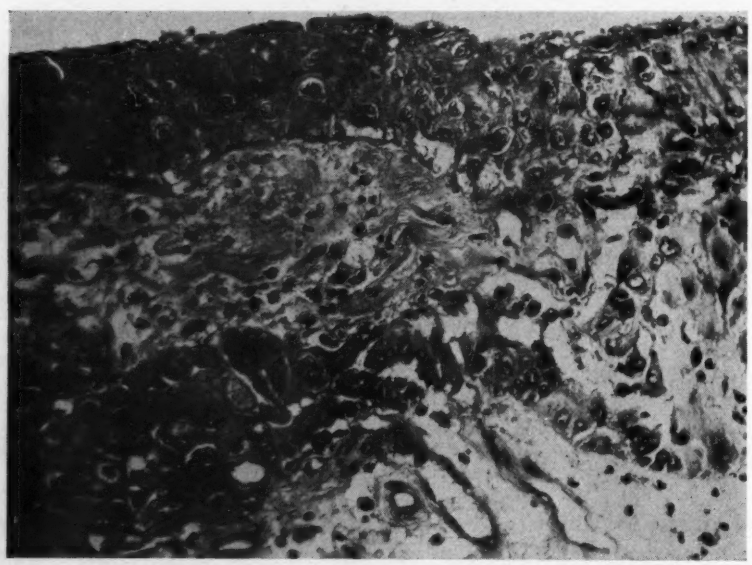


Fig. 15.—Case 15. An intraepithelial carcinoma is noted in the lining of the cyst wall. Beneath this can been seen a rather anaplastic epidermoid carcinoma lying in the stroma of the cyst wall.

Pathology Report.—(Ovarian Tumor Registry No. 91.) The specimen consisted of a large tumor mass measuring 14 by 9 by 9 cm., at one end of which was a large cystic area 12 cm. in diameter which was doughy and fluctuant. The outer surface was smooth and glistening over the greater part of the specimen. The opposite end was firm and resistant.

On cut section the cystic structure was found to contain large amounts of yellowish lipoid material embedded in which there were masses and nests of hair. Cut surface of the other portion of the lesion showed some fibrous tissue stroma but the major part was cellular.

Impression.—Dermoid cyst of the ovary with anaplastic squamous-cell carcinoma; acute and chronic salpingitis.

CASE 15.—(Courtesy of Dr. J. Herman Long, Baltimore, Maryland.) Miss M. B., a 44-year-old nullipara, was admitted to Johns Hopkins Hospital in August, 1952, because of abdominal enlargement of 4 months' duration.

Laparotomy showed a large smooth cyst arising from the left ovary which was fairly free except posteriorly where it was densely adherent to the rectum and sigmoid. There was a surgical absence of the uterus, tubes, and right ovary. A left oophorectomy and colostomy were performed.

Follow-up disclosed that the patient died of a recurrence of the carcinoma in February, 1953.

Pathology Report.—(JHH No. 103013.) The specimen consisted of a large cyst, opened prior to arrival in the laboratory, which must have measured 15 cm. when intact. The serosal surface was smooth and a mottled white-purple in color, the wall varying in thickness from 1 mm. to 4 cm. On the inner surface there were numerous papillary excrescences, some of which were hemorrhagic.

Microscopic examination showed that there were areas of carcinoma in situ in the stratified epithelium. The connective tissue stroma was invaded by nests and cords of a very anaplastic squamous-cell carcinoma which in some sections was seen extending from the stratified squamous lining.

Impression.—Squamous-cell carcinoma arising in a dermoid cyst.

Incidence

As rather scant attention has been directed toward carcinomatous degeneration of benign cystic teratomas, few series are large enough to be of value in determining the incidence of this complication. Miller,[9] by combining the reports of eleven different authors, found 22 primary carcinomas in 1,268 benign cystic teratomas, an incidence of 1.7 per cent. Our recent survey of 1,007 cases uncovered 8 carcinomas, a frequency of 0.8 per cent. Higher incidences noted by Kent[5]—8 per cent, MacCarty and Sistrunk[8]—7 per cent, Rohdenberg[13]—6.6 per cent, Lippert[7]—3 per cent. and others were all derived from rather small groups of cases and cannot be considered statistically significant. Further investigations based on large numbers of carefully examined cysts are needed before an accurate figure can be determined. At present the incidence of carcinoma arising in benign cystic teratomas must be placed in the neighborhood of 1 per cent, although it is our impression that more detailed studies will reveal that it is in reality higher than this.

Age

A benign cystic teratoma may undergo carcinomatous degeneration at almost any age, although the range in our series was 31 to 78 years. That reported in the literature is 19[2] to 88[1] years. The average age at the time of diagnosis in our group was 50.6 years, which is only a slight deviation from the 49 years reported by Alznauer.[1] Approximately 71 per cent of our cases occurred in women over 40 years of age, although the peak incidence was in the fourth decade—4 cases. These figures are somewhat at variance with those reported in the literature for here we note a peak incidence in the fifth decade and 70[9] to 80 per cent[1] of the cases diagnosed after the fortieth year of age. It is hoped that our figures represent a trend toward earlier diagnoses rather than a rise in the incidence of carcinomatous degeneration in younger women.

Symptoms

There are no symptoms which would lead one to suspect malignant degeneration of a benign cystic teratoma until extension beyond the cyst has occurred. Reviewing the histories of our patients we find that their symptoms were essentially the same as one would anticipate in ovarian cysts in general. Pain was present in 66 per cent and abdominal enlargement in 50 per cent of the cases. Other less common complaints were weakness, urinary frequency, and constipation. The duration of symptoms varied from a few hours to seven years, although generally the complaints were of two to three months' duration by the time the patient was admitted to the hospital. Of interest was the finding that two patients were completely asymptomatic and the cysts were found only by routine examination.

Pathology

Although carcinomatous degeneration of a benign cystic teratoma occurred more frequently on the right side than on the left, 8 cases versus 6, we feel that this represents a sampling error, especially as a review of the literature tells us that the incidence is about the same on each side. Of perhaps more interest are the 2 patients with bilateral benign cysts in which one of each had carcinomatous degeneration. It has been emphasized that malignant degeneration occurs more frequently in bilateral benign cystic teratomas than when they are unilateral.[4, 6] This does not appear to be substantiated by our series for the incidence of bilaterality among cysts with carcinomatous degeneration was 13.3 per cent which compares with Miller's incidence of 15.1 per cent in 963 benign cysts.

The size of the cyst which gave rise to carcinomatous degeneration, at the time of removal, varied from 10 to 26 cm. with an average of 16 cm. This indicates that malignant degeneration is more common in the larger-than-average cyst, a finding borne out by the literature. Unfortunately, this is only a rule of thumb for a number of cases of carcinomatous degeneration of benign cystic teratomas have been reported wherein the cysts were only 5 to 10 cm. in size; a group which accounts for 60.5 per cent of all of these benign tumors, according to our recent survey.

A review of the pathological descriptions in our case reports will give an idea of the variation in the gross characteristics of carcinomatous degeneration of benign cystic teratomas, ranging from those which permit a diagnosis from the gross specimen to those which present a rude surprise by the microscope. In two of our cases the malignancy was not suspected until the tissue was submitted to microscopic examination, and even at this time the carcinoma was found in only a small area of an individual slide. This clearly emphasizes the necessity for careful sectioning of these cystic tumors. The "dermoid plug," or mamilla, is very often the site of carcinomatous degeneration and representative sections should always be taken of this area, even though it appears grossly normal. In addition, any thickened, nodular, or papillary area in the cyst wall calls for careful investigation. It is by these measures only that we will be able to discover the early carcinomas in these cysts and institute proper therapy. The apparent benignity of an adult cystic teratoma should never be allowed to induce a false sense of security, for in truth it cannot be labeled benign, or adult, until proved so by careful microscopic examination of several representative sections.

Microscopically one almost invariably finds epidermoid carcinoma although adenocarcinoma has been reported. The epidermoid carcinoma seems to show the same degrees of differentiation that are seen when it is found in the vulva, accordingly, the basal-cell variety is uncommon. This range of differentiation

is exemplified by the difference in the histological pictures in Case 8 and Case 4. In Cases 3 and 15 we noted an intraepithelial carcinoma in one area which was found to extend on into invasive squamous-cell carcinoma in other sections. This suggests that any hyperactivity in the squamous epithelium requires further investigation before carcinoma can be excluded.

Treatment

Operation is the only therapy, at the present time, that offers the patient any hope of cure of this disease. Analyzing the results in our admittedly small group of cases, we find that the most favorable results were obtained when the uterus and adnexa were removed, and removed without rupture of the cyst. This finding is in accordance with the reports of others.[11, 14] Unfortunately, however, many cases are not diagnosed until the patient is in the postoperative period and unless total surgery has already been performed, one is faced with the dilemma of whether to reoperate or to watch the patient. This question is sorely in need of a clinically substantiated answer, but until this is provided, it appears that the wisest course would be reoperation and complete removal of the remaining pelvic organs. In those cases where the diagnosis is made at initial operation, either by frozen section (Case 5) or/and by the gross appearance, the surgeon should proceed with total removal of the uterus and adnexa.

We wish to emphasize the necessity for careful inspection of the neighboring tissues whenever the cysts wall appears to have been penetrated or whenever there are very dense adhesions. Any suspected lesion should be biopsied with frozen section if the surgeon is in doubt as to its nature. The importance of this becomes evident when one reviews the salvage of those patients with metastatic lesions. Every patient with metastasis in our series died within a short period of time, an observation reported by others.[1, 3] Whereas a somewhat hopeful prognosis may be given in the absence of extension, those patients with metastases that are not resectable or are overlooked can be expected to die of the malignancy within a year or two. One is therefore obligated to remove any of these metastatic lesions until a more valuable method of treatment becomes available, even though the results with this method of treatment are far from satisfactory.

The salvage in one case (Case 12) in which a simple salpingo-oophorectomy was performed permits the suggestion of a small note of optimism in some of these cases. Perhaps further investigation and experience will allow more conservative surgery in selected cases. In the light of present knowledge, however, a realistic attitude must label any approach less than radical a calculated risk.

The value of deep pelvic x-ray in the treatment of carcinomatous degeneration of a benign cystic teratoma is presently almost completely speculative. Admittedly, few cases have been reported wherein x-ray has been used postoperatively. In these instances, however its value was exceedingly dubious. It was used in only 2 of our cases and seems to have caused at most only a short delay in the death of the patients. It is hoped that, in spite of these initially poor results, x-ray will be used in the future in all patients with evidence of local spread of the carcinoma or in those in whom the cyst is ruptured during removal. By this course, the eventual place of x-ray in the treatment of carcinomatous degeneration of benign cystic teratomas can be accurately determined.

Prognosis

According to the literature[1, 11, 14] the prognosis is extremely grave in the presence of malignant degeneration of benign cystic teratomas. Analyzing our series of cases we have 13 patients available for follow-up study. Reference to Table I will show the results in these patients.

TABLE I. RESULTS OF FOLLOW-UP STUDY OF 13 PATIENTS WITH MALIGNANT DEGENERATION OF BENIGN CYSTIC TERATOMAS

	METASTASIS	RUPTURE	NUMBER	PER CENT
Alive 5 or more years	0	0	4	30.8
Alive 4 or more years	0	0	1	7.7
Died of other causes	0	0	1	7.7
Died or would have died of malignancy	4	3	7	53.8
No follow-up	0	0	2	—

Although this is too small a series of cases from which to draw valid conclusions, it does indicate a different trend from the 85 per cent mortality reported by Alznauer, as well as the mortality rates noted by other authors.

Two factors stand out as being important in evaluating the prognosis in this disease—metastasis and rupture of the cyst. These conditions were present in 7 of our series and in each case the patient succumbed to the malignancy within a few months with the exception of Case 7 who lived for two years before she died of a recurrence of the carcinoma. In one other case (Case 14) the patient had inoperable carcinoma and although she died in shock 96 hours after operation it is felt that she would not have survived more than a short while and therefore is included in this group of cases.

The 6 patients without evidence of extension of the malignancy beyond the cyst, all survived with the exception of one who died six months after operation of other causes. One patient in this group lived 14 years before dying of other causes, 3 are still alive 7 years after operation, and one is alive 4 years after operation. One might infer from these results that an excellent prognosis might be expected in this group. However encouraging this reasoning maybe, we must await further experience before it can be considered other than wishful thinking.

Summary

1. Fifteen cases of epidermoid carcinoma arising in benign cystic teratomas are reported, each accompanied by a short case history and photomicrograph.

2. This complication, reported in about 1 per cent of all benign cystic teratomas, may be found to occur more frequently when these cysts are submitted to careful pathological examination.

3. The average age at the time of diagnosis was 50.6 years, with 71 per cent of the cases diagnosed after the fortieth year.

4. There are no symptoms that are indicative of malignant degeneration until extension has occurred.

5. In these cases the malignancy arose in 8 cysts on the right side, in 6 cases on the left, and in one case the side is unknown. In 2 instances the malignancy arose in one of bilateral cysts.

6. The pathology of the malignancy is briefly discussed and a photomicrograph of a representative area in each case is presented.

7. Emphasis is placed on the necessity for careful pathological examination of each cyst. One must never allow the apparent benignity of a cystic teratoma to cause a false sense of security for the cyst cannot be labeled benign until it is submitted to careful microscopic examination.

8. At the present time the treatment of choice is total removal of the uterus and adnexa in all but the very rare case.

9. In 7 cases either extension of the malignancy or rupture of the cyst was noted. Each of these patients succumbed to the disease in a short length of time.

10. Four patients have survived for 5 or more years—a salvage of 30.8 per cent.

We wish to express our appreciation to Dr. Emil Novak for his kindness in allowing us access to the Ovarian Tumor Registry. We further wish to extend our gratitude to the many physicians who permitted us to include their cases in this report.

References

1. Alznauer, R. L.: Am. J. Obst. & Gynec. 65: 1238, 1953.
2. Caillot, J., and Boulez, N.: Soc. d'obst. et de gynéc. de Lyon 23: 546, 1934.
3. Counseller, V. S., and Wellbrock, W. L.: Am. J. Obst. & Gynec. 28: 40, 1934.
4. Eisenstadter, D.: Monatsschr. Geburtsh. u. Gynäk. 54: 360, 1921.
5. Kent, C. F.: J. Missouri M. A. 33: 377, 1936.
6. Lapouge, C.: Arch. gén. de chir. 8: 769, 1914.
7. Lippert, W.: Arch. Gynäk. 74: 389, 1905.
8. MacCarty, W. C., and Sistrunk, W. E.: Surg., Gynec. & Obst. 17: 41, 1913.
9. Miller, J.: In Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, 1937, Julius Springer, vol. 8, sect. 3, pp. 693-701.
10. Novak, E.: Gynecologic and Obstetric Pathology, ed. 3, Philadelphia, 1952, W. B. Saunders Company, p. 368.
11. Peterson, W. F., Prevost, E. C., Edmunds, F., Hundley, J. M., Jr., and Morris, F.: Am. J. Obst. & Gynec. 70: 368, 1955.
12. Petrowa, E., and Karaewa, Ch.: Arch. Gynäk. 159: 422, 1935.
13. Rohdenberg, G. L.: J. Lab. & Clin. Med. 12: 211, 1926.
14. von Szathmary, Z.: Arch. Gynäk. 159: 689, 1935.

MYOBLASTOMA OF THE VULVA*

STEPHEN M. HANSON, M.D., AND CLAYTON T. BEECHAM, M.D.,
PHILADELPHIA, PA.

(From the Departments of Pathology, Obstetrics and Gynecology, Temple University School of Medicine and Hospital)

GRANULAR-CELL myoblastoma, a usually unicentric, usually benign tumor, was first reported by Abrikossoff[1] in 1926. Since then it has occupied a prominent place among those tumors whose morphology is so distinctive that it is difficult to mistake them, but whose cell of origin remains the subject of much discussion, the chief theories advanced in this instance being striated muscle, histiocytes, fibroblasts, and peripheral nerve. It is not a common tumor, Murphy, Dockerty, and Broders[17] in 1949 being able to find only 219 reports of its occurrence in the literature, to which they added 10 of their own. In their series about one-third of the cases occurred in the tongue, with the skin, breast, subcutaneous tissues, and maxilla making up another third. Since that time the number of reported cases has risen to well over 300.[3, 4, 10, 18, 22] *Of these, we have been able to find only 10 which occurred on the vulva.*[4, 13, 14, 17, 23, 25-29] Because of its rarity in this location and because of the interest of this lesion, we wish to add 2 cases of our own. In addition, we are able, through the kindness of Dr. J. Y. Clarke,[7] to furnish details of a case which has previously been mentioned by Sadler and Dockerty.[23]

CASE 1.—Mrs. M. S., a 54-year-old para iv, gravida iv, white housewife, four years past the menopause, was admitted to Temple University Hospital on Aug. 15, 1953, with a chief complaint of vulvar tumor. This lesion was described as being the size of a pea when first noticed by the patient on the right labium majus a year prior to admission. In the ensuing year the lesion grew slowly, with occasional itching. During the last few months the patient had experienced occasional sharp but fleeting pains in the right groin. On physical examination at admission, a 2 by 3 cm. firm, nontender nodule, fixed to the skin but with no ulceration, was noted on the right labium majus. The regional lymph nodes were not palpable. The vagina had good support. The cervix was clean and well epithelized. The corpus was of normal size and the adnexa without palpable masses. The admitting impression was hydradenoma or carcinoma. At operation on Aug. 18, 1953, the tumor was removed, together with most of the labium majus, by elliptical incisions which left a wide margin of normal tissue on all sides and deep to the tumor. Recovery was uneventful and the patient was discharged on Aug. 21, 1953. Examination of the area after one year showed no recurrence of the tumor.

The pathology report was as follows:

Gross.—The specimen consisted of a section of skin and subcutaneous tissue. The skin surface measured 5 by 7 cm. In the center of the skin was a firm subcutaneous nodule slightly more than 2 cm. in diameter. The nodule bulged from the surrounding surface and was tightly adherent to the skin over it. On cut section it could be seen to be composed

*Presented at a meeting of the Obstetrical Society of Philadelphia, Nov. 4, 1954.

Fig. 1.

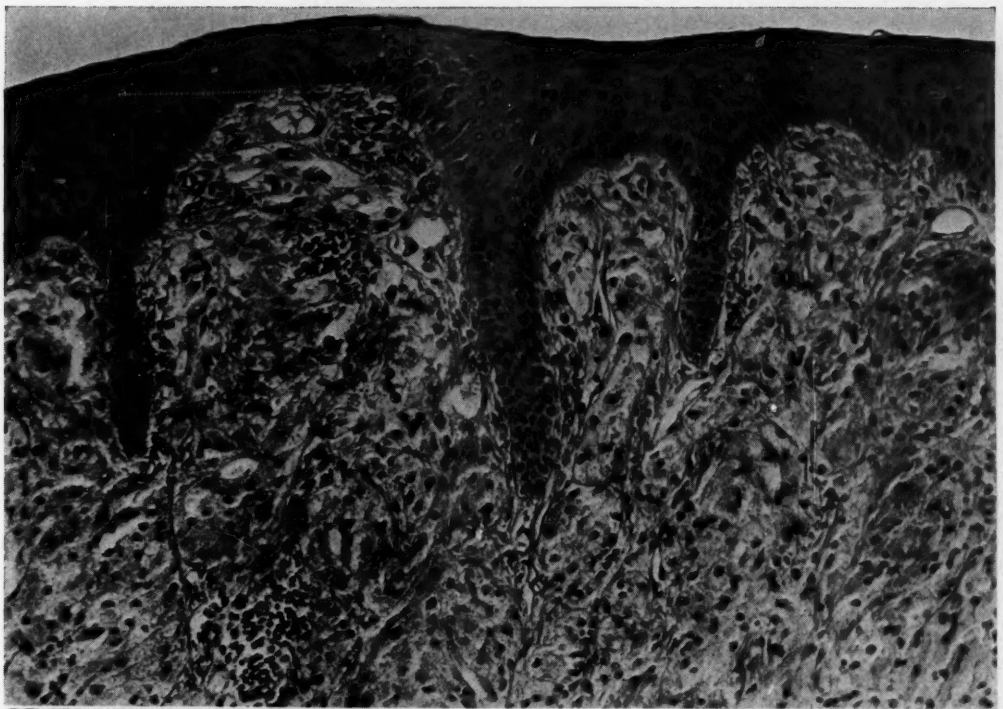


Fig. 2.

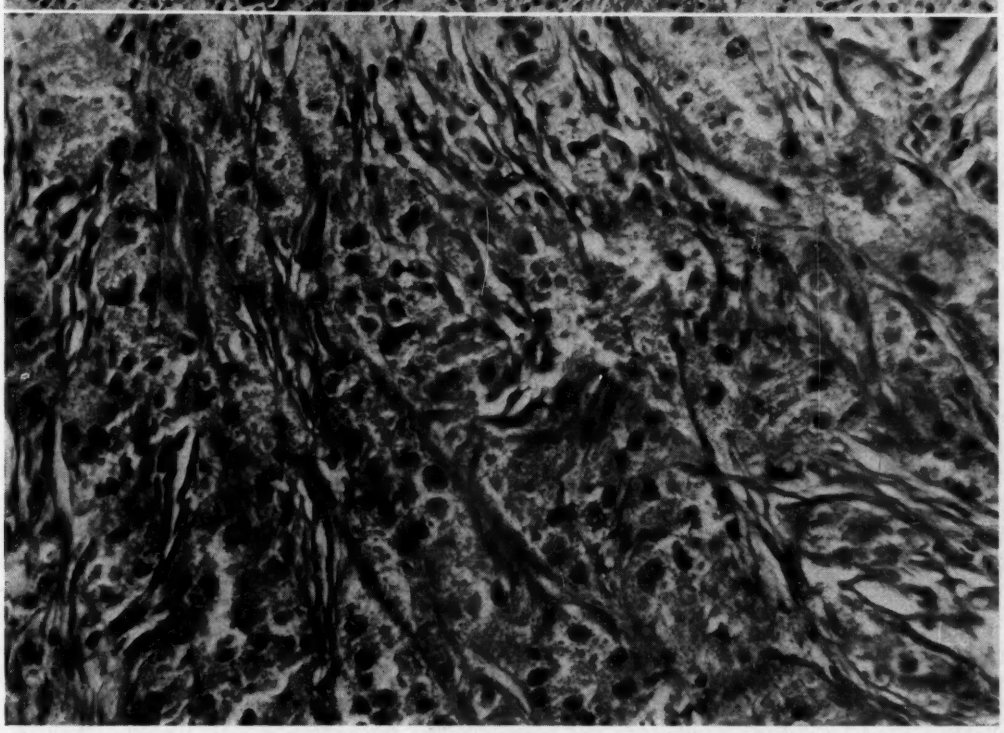


Fig. 1.—Section of the first myoblastoma reported in this article. Note the intimate relationship of the tumor to the epidermis. (×200; reduced ¼.)

Fig. 2.—High-power view of the same lesion. Note the granular cells typical of uniform myoblastoma separated by thin strands of fibrous tissue. (×440; reduced ¼.)

of yellowish tissue with interlacing white fibrous strands. The measurements across the greatest diameters were 2.0 by 2.3 cm. There was no capsule. The deep surface of the specimen was grossly free of tumor.

Microscopic.—The sections showed tumor tissue. The neoplasm was covered on one surface by a layer of squamous epithelium and on its opposite or deeper surface by a wide band of fatty tissue containing blood vessels and prominent fibrous trabeculae. The periphery of the tumor was sprinkled with adult lymphocytes. At one edge of the specimen there was a segment of normal epidermis and subcutaneous tissue. The squamous epithelium overlying the tumor was relatively thin, although the rete pegs were somewhat narrowed and elongated; this was not the pattern of pseudoepitheliomatous hyperplasia. The neoplasm was unencapsulated and poorly circumscribed, showing irregular extension into the fatty tissue. The tumor had a distinctive pattern and cytoarchitecture. It was composed of alveolar septate collections of large cells with abundant granular cytoplasm; in some areas the cytoplasmic borders were indistinct and were merged to form syncytial backdrops. The nuclei, while relatively uniform in size, were variable in shape and staining quality. Many were small, round, and dark, while others were larger, elongated, and vesicular. Some of the larger, paler nuclei contained a single nucleolus, which was central or eccentric in location. No giant cell formation and no mitoses were encountered. The alveolar septate pattern was produced by thin or coarse collagenous strands, which in some places resulted in a cordlike distribution of the cells and in other areas led to lobular syncytial groups. The neoplastic cells approached the basal layer of the epidermis, but did not disturb this layer in any detectable fashion, except perhaps to cause slight thinning and narrowing and elongation of the rete pegs, as mentioned. The histopathological picture was interpreted as the uniform type of granular-cell myoblastoma. There was nothing in the material examined which would give a clue as to the genesis of this particular lesion.

CASE 2.—Mrs. L. W., a 39-year-old para 0, gravida 0, Negro housewife, entered Temple University Hospital on March 16, 1954, with a chief complaint of "growth on the vagina." She had first noticed a small knot on the left side of the perineal area about six months prior to admission. There had been no marked change in size of the lesion. Pain had never been present, but intermittent itching had occurred. On physical examination at admission, a 2.5 by 2.0 cm. firm, nonulcerated, nontender mass, fixed to the skin, but movable over the deep structures, was noted on the left labium majus. The regional lymph nodes were not palpable. The vagina was clean and had good support. The cervix was completely epithelized. The system review and past medical history were noncontributory; the general physical examination was essentially negative. The admitting diagnosis was "mass in the substance of the left labia, etiology to be determined." On March 17, 1954, the mass was removed by local excision. Upon report by the Pathology Department that tumor cells were present in the edge of the surgical specimen, the patient was subjected to a left vulvectomy on March 22. Recovery from this procedure was uneventful, the patient being discharged on March 27, 1954. Examination after six months showed no evidence of recurrence of this lesion.

The pathology report was as follows:

Gross.—The specimen consisted of an elliptical piece of skin measuring 4.0 cm. by 2.5 cm. Attached to this was a fragment of subcutaneous tissue measuring 1.3 cm. in thickness. On section, there could be seen in this tissue an indurated, unencapsulated nodule measuring 2.5 cm. by 2.0 cm. in its greatest diameters. This nodule varied in color from grayish white to light yellow.

Microscopic.—Multiple sections taken of this lesion showed a similar picture throughout all slides. The significant sections disclosed neoplastic proliferation, which presented a uniform cytoarchitecture. There were nests and cords of large, pale cells embedded in and separated from one another by bands and strands of dense collagenous tissue, which imparted an indistinct alveolar-septate pattern to the process. The tumor was poorly circumscribed and occupied the corium, both superficial and deep; in a few areas isolated groups of tumor cells penetrated the underlying adipose tissue. The neoplastic cells possessed abundant finely granular pink cytoplasm, the cell borders being frequently indistinct and merged, thus assuming a syncytial arrangement. The nuclei were somewhat variable; they were

Fig. 3.

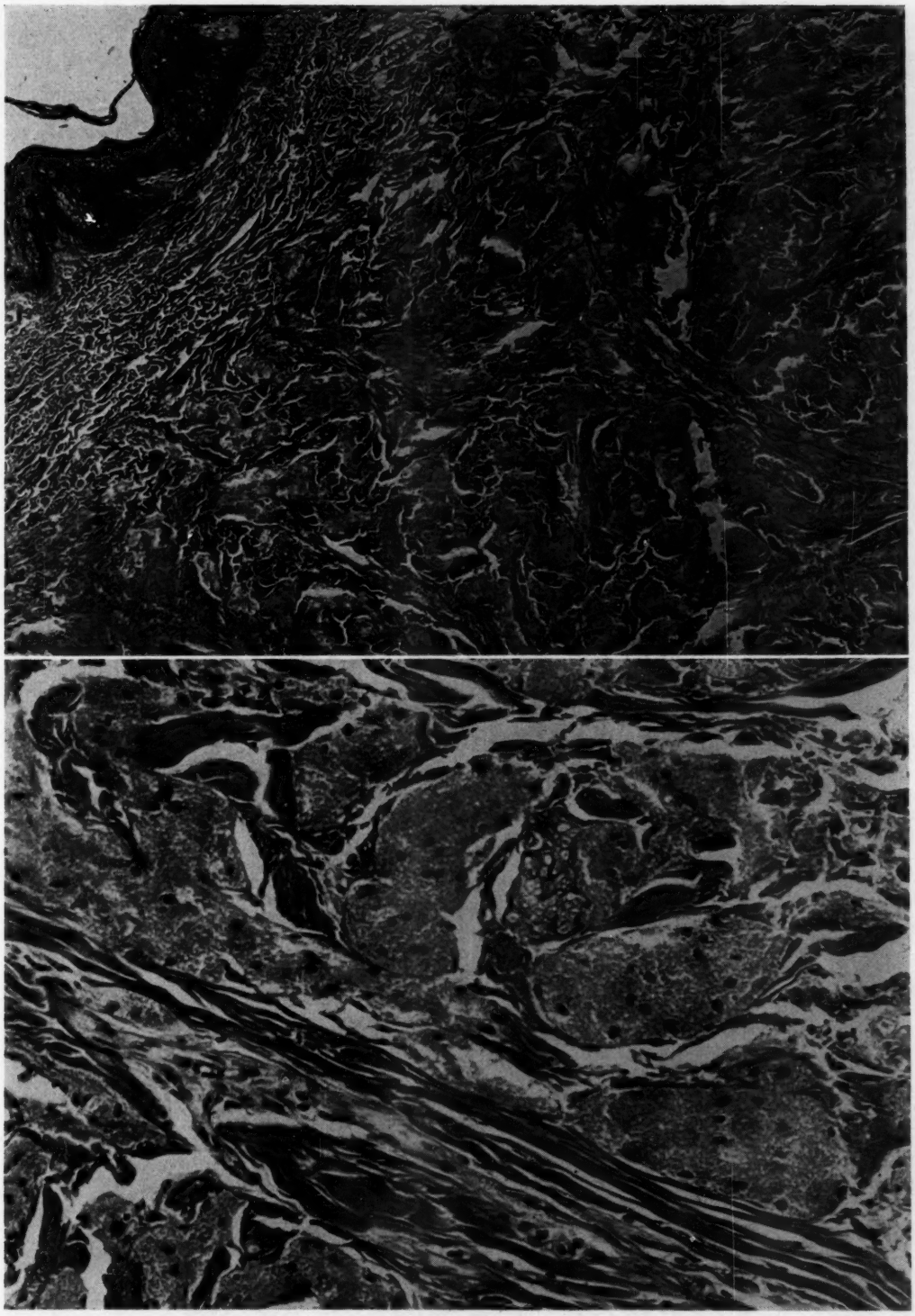


Fig. 4.

Fig. 3.—Section of the lesion of Case 2. Note that the fibrous stroma is more dense than in Case 1. This is a factor of considerable variability in myoblastoma. (×72; reduced ⅙.)

Fig. 4.—Higher-power view of Case 2. Note the large, granular tumor cells contiguous to a small nerve. (×255; reduced ⅙.)

TABLE I. SUMMARY OF ALL REPORTED CASES

AUTHOR	AGE OF PATIENT IN YEARS	DURATION OF SYMPTOMS	SIZE OF LESION	SIGNS AND SYMPTOMS	TREATMENT	FOLLOW-UP
1. von Szathmary, 1937	32	Not known	"Pea sized"	Freely movable nodule under skin at anterior junction of labia minora. Discovered during examination of patient with prolapse of the uterus and cystorectocele	Local excision with recurrence in three months. Second lesion widely excised during vaginoplasty	Not given for second operation
2. Tamis and Kowles, 1941	39	3 years	2.5 cm.	Itching, hard, nontender nodule freely movable under skin of right labium majus	Excision	Well six months later
3. Murphy, Dockerty, and Broders, 1949	72	Not known. Patient senile	3.5 by 2.5 by 2.0 cm.	Hard, nontender, freely movable nodule in right labium majus. Discovered on routine physical examination	Excision	Not given
4. Kern, Kaufman, and Combes, 1950	25	1.5 years	1.8 by 4.5 cm.	Patient complained of slight pain on friction. Ulceration occurred four months prior to hospitalization. Lesion was an ulcer with a truncated granulomatous base and an elevated white, cordlike border. Was in the right inguinocrural groove adjacent to the lower pole of the labium majus	Wide, deep excision	No recurrence after three months
5. Irgang and Uttmann, 1951	25	2 years	3.5 by 2.5 by 2.2 cm.	Painless, itching, sharply demarcated, freely movable nodule attached to the skin of the lateral aspect of the lower one-third of the left labium majus	Excision	Not given

6. Wright, 1951	61	2 years	3 cm.	Irritating, hard, nontender lump in labium majus, attached to both skin and underlying tissues	Wide excision	Well one year later
7. Valentine and Thomas, 1953	54	2 years	2.0 by 2.0 cm.	Itching, freely movable, stony hard, nontender mass, which had been painful for two weeks. In the superior lateral portion of the right labium majus immediately under the skin	Local excision	No recurrence in three months
8. Sullivan, Malfetano, and Marsh, 1954	23	22 years	2 by 3 cm.	Hard, nontender, nonpainful raised area in superior third of right labium majus, covered by intact skin	Excision	No recurrence in five months
9. Clarke, 1954	14	6 weeks	2.8 cm.	Firm, spherical mass in labium majus. Surface of the tumor covered by mucous membrane, contained ulcerated area 5 mm. in diameter	Local excision	No recurrence after one and one-half years
10. Hanson and Beecham, 1954	54	1 year	2.0 by 2.3 cm.	Itching, firm, nontender nodule which had been painful for a few months. Fixed to the skin of the right labium majus	Wide excision	No recurrence in one year
11. Hanson and Beecham, 1954	39	6 months	2.5 by 2.0 cm.	Firm, nontender, itching mass fixed to skin of left labium majus, but freely movable over the deep tissues	Local excision, followed by vulvectomy	No recurrence after six months

single or multiple and a few possessed a tiny red nucleolus. Many of the nuclei were small, round, and dark, while others were larger and paler; occasionally, they became plump, elongated, and spindled. The cytoplasm, as indicated, was mostly finely granular, although occasionally its monotonous appearance was disturbed by the presence of larger eosinophilic masses, some of which approached the size of a red-blood cell. In one area the tumor cells were immediately contiguous to a nerve fiber, but whether this represented invasion or origin was difficult to decide. Although tumor cells approximated the epidermis, no evidence of pseudoepitheliomatous hyperplasia could be seen. No Touton giant cells were encountered; fat stains were not done. The histopathological picture of this lesion was characteristic of so-called granular-cell myoblastoma. No tumor cells were encountered in the tissue from the re-excision of this lesion.

Of the ten additional cases in the literature, eight have previously been described in detail. These are summarized in Table I, together with the case of Clarke and our own two cases.

Discussion of Cases

The age limits of 14 and 72 years and the average age of 39 are in agreement with the finding in 229 cases of myoblastoma[17] that the peak incidence is in the third, fourth, and fifth decades, but that they may occur at any age. The clinical stories in all cases are similar, the patients reporting a painless, slowly growing, firm, nonfluctuant nodule, which was found to be either fixed to the skin or freely movable in the subcutaneous tissues. These growths were so little alarming that in most of the cases there was patient delay of more than a year after awareness of the tumor, the onset of pain or ulceration finally bringing the patient to the doctor in about half of the cases. These last symptoms were apparently due to the mechanical effect of the enlargement of the tumors, as pain is not a characteristic feature of myoblastoma, and ulceration carried with it no connotation of malignant change in these cases. In support of this view is the relatively constant size of the tumors when first seen, the smallest for which we have accurate measurements being 2.0 cm. by 2.0 cm., and the largest 3.5 cm. by 2.5 cm. Although itching was noted in half of the cases in which there was awareness of the lesion, this is so common an accompaniment of vulvar pathology that it is doubtful that much significance can be attached to it.

In all cases in which follow-up is available, local adequate excision of these lesions was curative. In 1951, Sadler and Dockerty[23] reported as a malignant myoblastoma a vulvar tumor which recurred three times after local excision, each time appearing more malignant histologically. The original diagnosis by the patient's local physician had been an "infected sweat gland cyst" of the left labium majus. We have examined the slides of this case through the courtesy of Dr. Dockerty and feel that, while it may be classified as a pleomorphic myoblastoma by those[17] who feel that there is a very close association between pleomorphic myoblastoma and rhabdomyosarcoma, it does not meet the criteria proposed by Ross, Miller, and Foote,[21] which we will discuss later. We prefer, therefore, to regard the tumor of Sadler and Dockerty as a myosarcoma, probably a rhabdomyosarcoma, although examination of many fields failed to reveal the presence of striations. It is unfortunate that the tissue from the original lesion in this case was never available for microscopic study.

Gross Appearance and Histopathology.—

Grossly, benign, or uniform, myoblastoma is a firm tumor of uniform consistency. No capsule is evident, the edges of the tumor blending with the surrounding tissue. On cross section, interlacing white fibrous bands surround small areas of softer yellow tissue. Degenerative changes are uncommon. Microscopically, the tumor is composed of irregular strands or fascicles of

granular cells. These strands and fascicles are separated by varying amounts of fibrous tissue. From the heavier columns of fibrous tissue, smaller strands project so that the groups of cells are enmeshed in a diffuse network of collagenous and reticular tissue. In some instances the cells have distinct borders, while in other areas it may be impossible to distinguish individual cell outlines, the cells of a fascicle taking the appearance of a syncytium—a multinucleated granular protoplasmic mass. There is no capsule, cords of the cells at the margins of the tumor projecting into the adjacent fibrous tissue. The granules, which are the distinctive feature of a myoblastoma, vary considerably in size and have been classified by Bangle[4] into fine, coarse, and conglomerate, with fine the most common. The conglomerate may surpass the size of a red blood cell. The nuclei, which are not characteristic, vary somewhat in size and shape, being round or oval and containing finely granular chromatin. An unexplained feature of these lesions is the downward proliferation of the covering squamous epithelium in some instances to such an extent that it may resemble well-differentiated squamous-cell carcinoma. This has been termed "pseudoepitheliomatous hyperplasia."

Histogenesis.—

The theory of the derivation of these tumors from striated muscle originally proposed by Abrikossoff[1, 2] was for years the most strongly supported,[8, 12, 15, 17] although a few authors[16, 20] suggested that these tumors were composed of histiocytes, and that the granules represented stored material. In late years, however, these theories have been overshadowed by that first proposed in 1948 and 1949 by Fust and Custer[9, 10] who after studying a number of these tumors concluded that they were of neural origin and proposed the name "granular-cell neurofibroma." In 1950, Pearse[18] reported finding the same relationship between nerves and tumor cells as described by Fust and Custer, but stated that he felt the tumor cells were fibroblasts and that the tumors were lipoid-containing granular-cell fibroblastomas. In 1952, both Ashburn and Rodger[3] and Bangle[4] wrote supporting the neural origin of these tumors but stating that they felt that the precursor cell—whether Schwann cell, fibroblast, or histiocyte—remained undetermined. The latter author[5] has been able to demonstrate a granular-cell "myoblastoma" entirely confined within a myelinated peripheral nerve. Additional support has recently been lent to the theory of neural origin by the report of Harland[11] of a large tumor of the hypophyseal stalk histologically showing all the features of granular-cell myoblastoma found elsewhere, and in this area being almost surely of neural origin.

Malignancy.—

Abrikossoff,[2] in his second paper on the subject, divided myoblastomas into four types, the first three of which were benign and the fourth malignant. In 1944, Howe and Warren[12] proposed a division of myoblastomas into "uniform," which was benign and corresponded to Abrikossoff's groups one to three, and "pleomorphic," which was malignant and corresponded to Abrikossoff's group four. This classification was used by Murphy, Dockerty, and Broders in their discussion of 229 cases. Numerous pleomorphic myoblastomas have been reported in the literature, but Ross, Miller, and Foote,[21] using the criteria that, unless a malignant tumor shows structural qualities described in Abrikossoff's first three groups in at least some parts of its primary, recurrent, or metastatic growth, it probably should not be considered a pleomorphic myoblastoma, were able to accept only 4 cases, to which they added 3 of their own. It was their feeling that the other tumors described as pleomorphic myoblastomas were either myosarcomas or the tumor described variously as "alveolar soft-part sarcoma"[6] and "malignant tumors of non-chromaffin paraganglia."[24] One of the cases accepted by these authors was that of

Powell,[19] in which there was involvement of both ovaries and the perineum together with multiple subcutaneous nodules and retroperitoneal tumor.

Summary

1. Since granular-cell myoblastoma was first described in 1926, more than 300 cases of this tumor have been reported, 10 of which have occurred on the vulva. We have added 2 additional cases.

2. The tumor occurs as a slowly growing, firm, nontender nodule either fixed to the skin or freely movable in the subcutaneous tissue. It may be present at any age, but is most common in the third, fourth, and fifth decades of life.

3. The histopathology is distinctive, there being irregular strands of large cells containing an abundant amount of granular eosinophilic cytoplasm, and separated by a fibrous network. The nuclei vary somewhat in size and shape, and their morphology is not pathognomonic.

4. The histogenesis of this tumor is disputed. It was originally believed to be derived from striated muscle. The concept of neural origin has recently received the strongest support, but the precise precursor cell—Schwann cell, histiocyte, or fibroblast—remains to be determined.

5. Wide local excision of the tumor is considered curative. Proved instances of malignant change in myoblastoma are few.

Addendum.—On the day we were checking the proofs of this article, our Pathology Department received a vulvar lesion of six months' duration from a 50-year-old Negro woman. This lesion was firm in texture, yellow in color, and firmly fixed to the overlying skin. It measured 2.5 by 2.0 by 1.5 cm. Upon microscopic examination, it has proved to be the third case of uniform myoblastoma of the vulva reported at Temple University School of Medicine and Hospital.

References

1. Abrikossoff, A.: Virchows Arch. path. Anat. **260**: 215, 1926.
2. Abrikossoff, A.: Virchows Arch. path. Anat. **280**: 723, 1931.
3. Ashburn, L. L., and Rodger, R. C.: Am. J. Clin. Path. **22**: 440, 1952.
4. Bangle, R., Jr.: Cancer **5**: 950, 1952.
5. Bangle, R., Jr.: Cancer **6**: 790, 1953.
6. Christopherson, W. M., Foote, F. W., Jr., and Stewart, F. W.: Cancer **5**: 100, 1952.
7. Clarke, J. Y.: Personal communication.
8. Crane, A. R., and Trembley, R. G.: Am. J. Path. **21**: 357, 1945.
9. Fust, J. A., and Custer, R. P.: Am. J. Path. **24**: 674, 1948.
10. Fust, J. A., and Custer, R. P.: Am. J. Clin. Path. **19**: 522, 1949.
11. Harland, W. A.: Cancer **6**: 1134, 1953.
12. Howe, C. W., and Warren, S.: Surgery **16**: 319, 1944.
13. Irgang, S., and Uttmann, R.: Harlem Hosp. Bull. **4**: 1, 1951.
14. Kern, A. B., Kaufman, J. J., and Combes, F. C.: Arch. Dermat. & Syph. **62**: 109, 1950.
15. Klemperer, P.: Am. J. Cancer **20**: 324, 1934.
16. Leroux, R., and Delarue, J.: Bull. Assoc. franç. étude cancer **28**: 427, 1939.
17. Murphy, G. H., Dockerty, M. B., and Broders, A. C.: Am. J. Path. **25**: 1157, 1949.
18. Pearse, A. G. E.: J. Path. & Bact **62**: 351, 1950.
19. Powell, E. B.: Arch. Path. **42**: 517, 1946.
20. Ringertz, N.: Acta path. et microbiol. Scandinav. **19**: 112, 1942.
21. Ross, R. C., Miller, T. R., and Foote, F. W., Jr.: Cancer **5**: 112, 1952.
22. Rothchild, T. P. E., and Crary, R. H.: Ann. Surg. **137**: 530, 1953.
23. Sadler, W. P., and Dockerty, M. B.: Am. J. Obst. & Gynec. **61**: 1047, 1951.
24. Smetana, H. F., and Scott, W. F., Jr.: Mil. Surgeon **109**: 330, 1951.
25. Sullivan, Thomas F., Malfetano, J., and Marsh, M. R.: Am. J. Obst. & Gynec. **67**: 687, 1954.
26. von Szathmary, Z.: Ztschr. Geburtsh. u. Gynäk. **114**: 371, 1937.
27. Tamis, A. B., and Kowles, J. J.: Am. J. Obst. & Gynec. **42**: 543, 1941.
28. Valentine, F. M., and Thomas, J. R.: Am. J. Obst. & Gynec. **65**: 213, 1953.
29. Wright, J. L.: New Zealand M. J. **50**: 560, 1951.

ARTERIOVENOUS SHUNTS IN THE MYOMETRIUM*

GEORGE P. HECKEL, M.D., AND CHARLES E. TOBIN, PH.D., ROCHESTER, N. Y.

(From the Department of Obstetrics and Gynecology and the Department of Anatomy, the University of Rochester School of Medicine and Dentistry)

ARTERIOVENOUS shunts in the endometrium of the human uterus, first described by Schlegel,[1] have since been recognized in the endometrium of nonpregnant and pregnant uteri by other investigators. Their presence in the uterine muscle was noted by the authors in the uterus of a 33-year-old woman who required hysterectomy because of intercyclic bleeding and menorrhagia which did not respond to endocrine treatment, and findings in 11 cases were reported.[2]

Since arteriovenous shunts are known to occur in the muscular part of other organs,[3, 4] the present investigation was undertaken to determine whether the demonstration of myometrial arteriovenous shunts (hereafter referred to as shunts) could be correlated with any physiological state or pathological condition.

Method of Study

The 25 uteri used in this study were obtained surgically from patients varying in age from 24 to 69 years (Table I). Within one to 24 hours after removal, the specimens were prepared by the methods and with the materials suggested by Tobin and Zariquiey.[5] Those few uteri which could not be injected within two hours after removal were stored in a refrigerator, but they were thawed out and warmed before injection. The technique consisted of the following procedures.

1. Cannulization, with glass cannulae, of the major branches of the uterine arteries and veins on the lateral borders of the specimens.
2. Perfusion of the arteries with normal saline solution until a relatively clear perfusate returned from the veins. During perfusion any leaks from the cut ends of the smaller vessels or through the walls of the larger vessels were stopped by clamps or ligatures.
3. Acetone was perfused via the arteries into and through the veins.
4. Glass spheres, 200 ± 25 microns in diameter, were poured into the arterial cannulae.
5. A red solution of vinyl acetate was injected into the arteries and a blue solution of this liquid plastic into the veins.
6. The perfusion and injections were made with a Janet-Frank bladder syringe connected by rubber tubing to the glass cannulae in the arteries and veins. Pressure ranges for the injection varied from 50 to 200 mm. Hg.
7. Samples of representative areas were removed from the injected uteri, fixed and sectioned by the usual histological methods for microscopic study of the uterine tissue.
8. The remaining uterine tissue was removed from the vascular casts by macerating the specimens in concentrated hydrochloric acid. After maceration the vascular casts were washed in running water, allowed to dry by evaporation of the water from the casts, and then studied under a dissecting microscope.

*This project was supported in part by the Ernest L. Woodward fund.

TABLE I. CORRELATION OF ARTERIOVENOUS SHUNTS WITH PHYSIOLOGICAL AND PATHOLOGICAL CONDITIONS

CONDITION	NUMBER OF CASES	AGE RANGE	CASES DEMONSTRATING SHUNTS
Normal uterus			
Normal menstruation	3*	34-48	1
Postmenopausal	3	50-69	1
Menorrhagia	6	26-36	4
Fibroid uterus			
Normal menstruation	3	27-44	2
Menorrhagia	4	35-44	3
Other abnormal bleeding	2	40-54	1
Pregnancy	4	24-37	4
Parous uterus (nonpregnant)	17		12
Nulliparous uterus	5		1
Uterus with premenstrual secretory endometrium	6		4
Uterus with nonsecretory endometrium	9		5
Condition of endometrium not determined	11		7
Uterus bleeding at time of hysterectomy	2		1

*Operation was done because of pelvic pain.

Observations

Shunts, larger than capillaries, were found in the vascular casts between branches of the uterine arteries and veins both within the myometrium and the endometrium in 16 of the 25 specimens. These vascular casts demonstrate very well the course and shape of the veins (Fig. 1), which unlike the arteries are not coiled in the myometrium and form roughly circular or irregular sinusoids. The coiled nature of the arteries both within the endometrium (Fig. 2) and in the myometrium (Fig. 3) are also well demonstrated. The apparently excessive coiling of the arteries may be partly artifactitious due to the contraction and skrinkage of the specimens during preparation. Like arteries in any other distensible viscus, however, their coiling may be necessary to allow for distention of the uterus without partly occluding the arteries, or they may be instrumental in regulating the arterial pressure to smaller vessels in the uterine tissue.

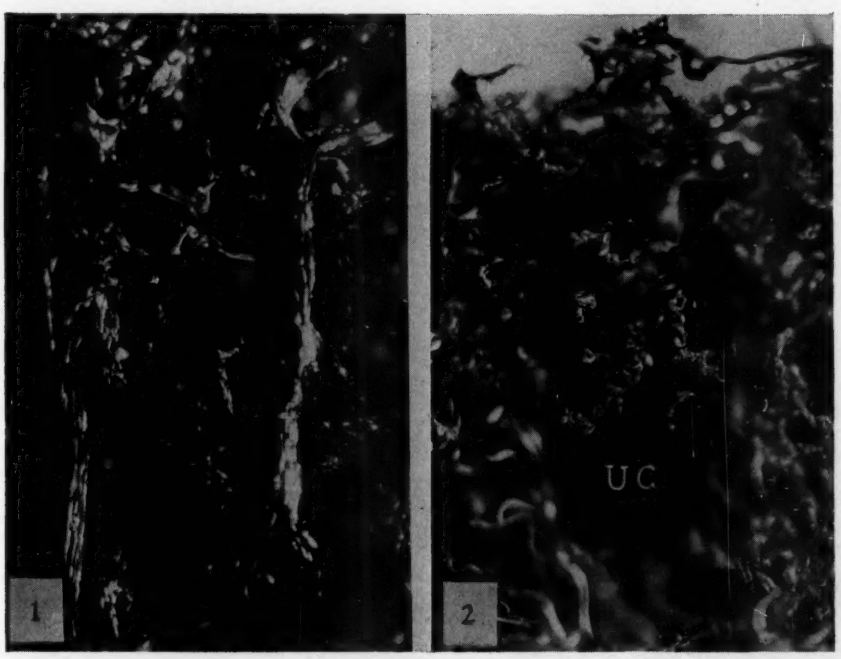


Fig. 1.—Vinyl acetate casts of the uterine veins from the myometrium showing the circular form of the smaller veins. Following injection of the plastic into the uterine vessels the tissue was digested away with concentrated hydrochloric acid. (×7; reduced ⅙.)

Fig. 2.—Vinyl acetate casts of the uterine veins and arteries of the myometrium and endometrium obtained by injecting red plastic into the arteries and blue plastic into the veins. Reproduction in black and white of the Kodachrome photograph makes the veins appear dark and the arteries light. Note the coiled nature of the arterial casts from the endometrial area adjacent to the uterine cavity (*UC*). (×7; reduced ⅙.)

The cases demonstrate the course, form, and relations of the arteries and veins, and the anastomoses between branches of the arteries and veins. A rough estimate of the diameter of the shunts was gained by the passage into the veins of the glass spheres (Fig. 4). The location of the shunts was demonstrated by the point of admixture of the two colors of plastic in the vessels (Fig. 5). Since this plastic does not enter capillaries, it can be assumed that where admixture of the colors occurred the plastic must have traversed vessels larger than capillaries, just as glass spheres had to do.

Correlation of the clinical data with the presence of shunts is shown in Table I. The only condition in which they were found consistently was pregnancy. Of the 4 pregnant uteri studied, 2 were in the first trimester. The other 2 were obtained at term immediately following cesarean section. The free mixing of the plastic from arteries and veins in the dilated vessels of a uterus removed at cesarean section is shown in Fig. 6. Shunts were demonstrated in one of 4 apparently normal uteri from cases where there was a history of normal menstruation. They were seen in 4 of the 6 normal uteri where there was a history of menorrhagia. Shunts were present in about 70 per cent of the parous uteri, but in only one of 5 nulliparous specimens. Their incidence was about the same in uteri with secretory (premenstrual) and nonsecretory endometrium.

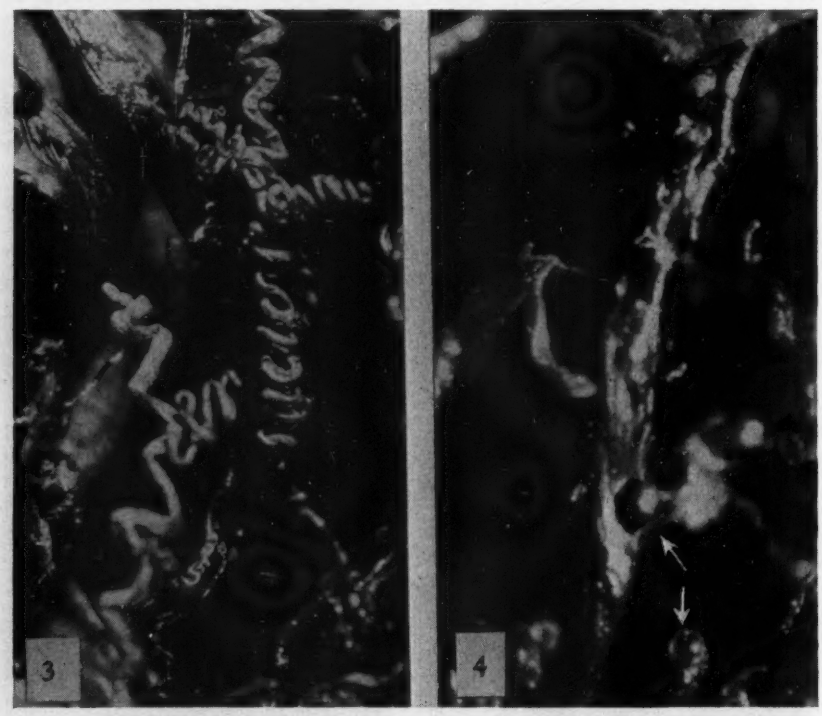


Fig. 3.—Casts of the coiled uterine arteries in the myometrium. (×15; reduced ⅙.)

Fig. 4.—Casts of uterine arteries (white) and veins (black) containing glass spheres 200 microns in diameter (indicated by white arrows). Note a glass sphere protruding through an arterial cast (lower center), and one in the venous cast. Since the spheres were included only with the red plastic injected into the arteries, they must have passed through openings at least 200 microns in diameter to gain entrance into the veins. Mixing of the different colors of plastic injected into the arteries and veins (upper center) indicates an arteriovenous shunt in the area. (×20; reduced ⅙.)

Shunts were found in the uterus of a 69-year-old woman who had had a hysterectomy because of intractable pelvic pain of undetermined origin and uterine tenderness. Slight bleeding, the first in 19 years, had occurred 18 days before operation. She had received estrogen of unknown amount within the previous nine months. The endometrium, however, showed no stimulation; it was senile in type. Although there was relatively free mixing of the plastic from arteries and veins, indicating numerous shunts in this uterus, there was nothing to suggest arteriovenous fistula, a condition which has recently been reviewed.[6, 7] In the vascular casts from the myomatous uteri, the incidence of shunts was about the same as in the normal specimens. These cases demonstrated that few branches of the uterine arteries penetrated into the interior

Fig. 5.—Cast of arteries and veins showing the location of a shunt (upper right) in the myometrium. The plastic does not enter capillaries. Thus the mixing of the red plastic (light on the photograph) injected into the arteries and the blue plastic (dark) injected into the veins indicates communications larger than capillaries between arteries and veins. (×10; reduced ⅙.)

Fig. 6.—Casts of the myometrial vessels from a term pregnant uterus. The location of the arteriovenous shunts, shown by the admixture of the injected plastic, are indicated by the arrows. Other shunts are also shown in the photograph. The degree of mixing in these large vessels and the finding of shunts in all of four pregnant uteri suggest that the shunts remain open during pregnancy. (×5; reduced ⅙.)

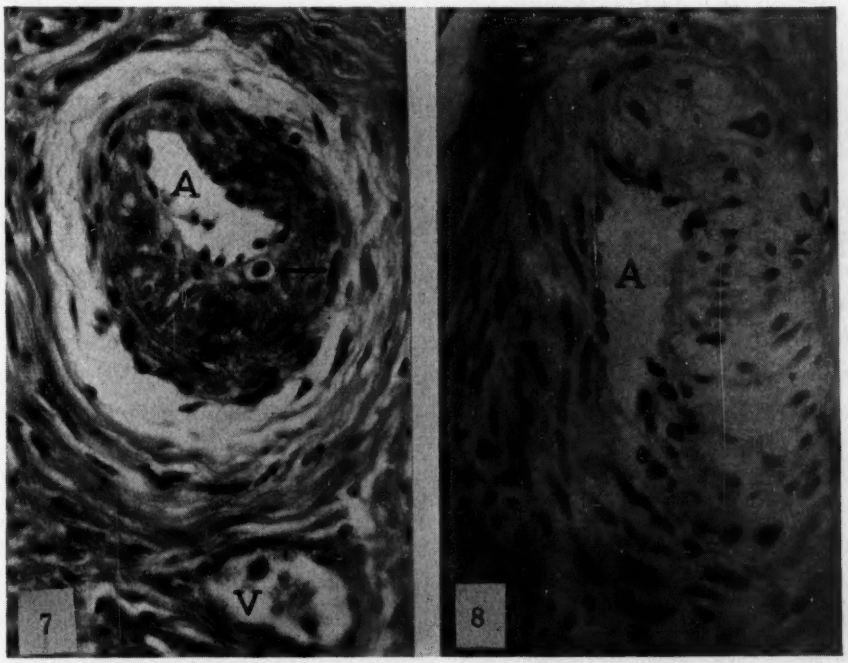


Fig. 7.—Section through the myometrium containing a branch of the uterine artery (*A*) and a branch of the uterine vein (*V*). The arrow points to an epithelioid cell in the smooth muscle of the arterial wall. The presence of this cell indicates that the vessel is part of an arteriovenous shunt. Compare Fig. 8. (×430; reduced ⅙.)

Fig. 8.—Section through the myometrium containing the arterial end (*A*) of an arteriovenous shunt. Note the large, clear, epithelioid cells in the smooth muscle of this vessel, at the top and to the right of this illustration. Compare with Fig. 7. These two figures demonstrate the difference in the number of epithelioid cells found in the wall of the arteriovenous shunt, and in the smaller arterial branches connected to the shunt. (×430; reduced ⅙.)

of the myoma, whereas large venous sinusoids were found around the periphery of the tumors. Plastic from the uterine arteries was found in the venous sinusoids, particularly in the area subjacent to the endometrium. This finding suggests that the shunts adjacent to the tumors, or in other parts of the uterus, increased their size by allowing near-arterial pressure to enter the sinusoids. The effect of the increased pressure would be greatest in the place of least resistance, within the endometrium between the myoma and the lumen of the uterus.

Examination of microscopic sections from tissue removed prior to digestion disclosed epithelioid cells (Figs. 7 and 8) in the walls of the vascular structures similar to those described for arteriovenous shunts in other organs. These structures, therefore, were assumed to be the shunts demonstrated in the vascular casts.

Comment

Since the presence of arteriovenous shunts in both normal and myomatous uteri appears certain, the question remains as to what might govern their normal and abnormal function. The nervous, humoral, or endocrine control of the uterine vessels (and the shunts) is not understood at present. The epithelioid cells which are present in the walls of the shunts have been reported to contain acetylcholine-like substances.[4] It may be that acetylcholine or some other cholinergic substance is liberated by the epithelioid cells to influence the functioning of these shunts, either directly by nervous control or through direct or indirect hormonal action.

It has been postulated that menstruation is started by the opening of the shunts in the endometrium. One can only speculate as to whether the myometrial shunts might behave similarly. It seems reasonable to suppose, however, that should the myometrial shunts remain open during and after the endometrial wound, when the endometrium had been partly shed, abnormally heavy bleeding would ensue. The pressure in the open venules without any contractile mechanism would be above normal, that is, somewhere between venous and arterial levels. One might further speculate that, should the shunts be open or closed to an abnormal extent, they might be in part responsible for abnormal congestion and pain as well as for profuse bleeding.

The shunts apparently remain open during pregnancy. Hertig and Rock[8] showed arteriovenous shunts to be adjacent to 11 and 12 day implanting ova. In the nonpregnant state the demonstration of shunts may be fortuitous, possibly depending on the condition of the shunts, at the instant of removal of the uterus. The rhythmic blushing and blanching of the endometrium observed by Markee[9] may be due to rhythmic opening and closing of the shunts in the endometrium. The myometrial shunts may have similar rhythmic activity. The phase in which activity stops, open or closed, when the uterus is removed may determine whether or not these shunts can be demonstrated by the injection of plastic.

It is well known that large and old myomas are relatively avascular. Faulkner,[10] utilizing a different injection technique for demonstration of the uterine vessels, showed that in the early stage of their formation fibroids contain many arteries which penetrate into their central core, but the veins are

found mainly around the periphery. Arteriovenous anastomoses were found in 4 of his 60 specimens, but this finding was explained as a result of injury to the specimen. He stated that "with relative anemia over a submucous myoma, it is evident that unless ulcerated, the uterine bleeding frequently accompanying such tumors does not come from the tumor itself, but is, when present, from the endometrium near-by which sometimes injects heavily with the venous mass."

The free mixing of plastic from both arteries and veins in the large venous sinusoids surrounding myomas indicated the presence of arteriovenous shunts. The profuse bleeding often associated with these tumors may result from erosion of the sinusoids lying beneath and within the endometrium, where the pressure would be considerably elevated as a result of the shunting of arterial blood into the sinusoids.

These myometrial arteriovenous shunts may also be the source of uterine arteriovenous fistulas under certain abnormal circumstances. In the gross pathology of the specimen described by Gaines and Greenwald,[6] the enlarged vessels were present mainly in the myometrium.

Summary

Arteriovenous shunts were found in the muscular portion of 16 of 25 surgically removed uteri.

These shunts were demonstrated by plastic casts of the vessels obtained by injecting arteries and veins with vinyl acetate of different colors. Glass spheres with a diameter many times that of capillaries passed from arteries into veins with the plastic.

In several myomatous uteri large venous sinusoids containing plastic from both arteries and veins were found around the periphery of the tumors, indicating that shunts were present.

Shunts were demonstrated in 4 pregnant uteri, but there was no perfect correlation of shunts with any other physiological or pathological condition.

The possible significance of these findings is discussed.

References

1. Schlegel, J. U.: Acta anat. 1: 284, 1945-1946.
2. Heckel, G. P., and Tobin, C. E.: Anat. Rec. 115: 395, 1953.
3. Prichard, M. M. L., and Daniel, P. M.: J. Anat. 87: 66, 1953.
4. Staubesand, J., and Genschow, C.: Ztschr. Anat. u. Entwcklngsgesch. 116: 446, 1952.
5. Tobin, C. E., and Zariquiey, M. O.: Proc. Soc. Exper. Biol. & Med. 75: 827, 1950.
6. Gaines, J. A., and Greenwald, J. C.: AM. J. OBST. & GYNEC. 65: 997, 1953.
7. Gardner, H. L.: AM. J. OBST. & GYNEC. 68: 845, 1954.
8. Hertig, A. T., and Rock, J.: Contrib. Embryol. 29: 127, 1941.
9. Markee, J. E.: Contrib. Embryol. 28: 219, 1940.
10. Faulkner, R. L.: AM. J. OBST. & GYNEC. 47: 185, 1944.

THE USE OF AUTOGENOUS ARTERIAL GRAFTS FOR THE EXPERIMENTAL RECONSTRUCTION OF FALLOPIAN TUBES

CLARENCE J. SCHEIN, M.D., F.A.C.S., AND RUTHVEN FERREIRA, NEW YORK, N. Y.

(From the Surgical Research Laboratory, The Montefiore Hospital)

A SERIES of experiments was initiated in September, 1953, in which exogenously vascularized blood vessel grafts were used to replace tubular structures conveying media other than blood. Such replacements of ureters and bile ducts are the subjects of separate communications.[11, 12, 13] This report is concerned with the experimental use of submucosally buried vascular grafts for the reconstruction of Fallopian tubes.

The significance of tubal obstruction as a factor in sterility and the poor results following the various types of tubal plastic procedures indicate the practical importance of this problem. It is not the purpose of this paper to review the clinical background, since this has already been so well done by Bohn and Englund,[1] Greenhill,[5] Lorset,[8] Rubin,[9] and Solomons.[10]

Ideally, the tubal replacement should provide a satisfactory conduit of adequate length, capable of peristaltic activity, and offer a favorable environment for the ovum while in transit. The use of an autogenous graft avoids the problem of antigenicity and foreign body reactions. The vascular graft has the disadvantage of lacking villi or fimbria and of producing no lubricating fluid. Burying the graft in a submucosal trough would seem to favor external vascularization of a graft which, unlike those conveying blood, must rely solely upon external sources for its nutrition. Israel's[7] experiments on dogs showing reconstitution of circular muscles eight weeks following total linear salpingostomy suggested that a buried graft, subsequently embraced by circular tubular muscle, might be peristaltically influenced. The use of the muscular tunnel theoretically also suggested the possibility of implantation of the graft into adjacent appendix, small bowel, or colon in those cases in which a bilateral salpingectomy had been performed. Inlay or onlay methods of graft implantation suggest a wide variety of morphologic distortions in which this method might still be technically practical.

Experimental Method

Nine female mongrel dogs ranging in weight from 16 to 26 pounds were anesthetized with intravenous veterinary Nembutal solution. Arterial grafts were obtained from either the splenic artery by a method previously described from this laboratory,[6] or from the carotid artery. In the dog we were able to utilize both carotid arteries, for bilateral reconstructions, with no apparent ill effect. Splenic artery grafts varied in size from 4 by 0.2 to 10 by 0.4 cm.; because of the small diameter we preferred using the carotid artery in the last 7 dogs operated upon. Carotid artery grafts varied from 7.6 by 0.3 cm.

to 9.5 by 0.5 cm. in size. To facilitate handling and anastomosis, all grafts were threaded onto polyethylene tubing and the graft manipulated via the tubing.

The abdomen was opened through a lower midline incision and the genital apparatus completely exposed. A wedge section of cornu was resected and the proximal end of the tube divided, doubly tied, and then peritonized on the body of the uterus below the sites of resection. The polyethylene tubing was threaded into the uterine cavity and over this splint an arterio-uterine anastomosis performed using continuous No. 5-0 chromic catgut on dual swedged needles.* The mesosalpinx was maintained intact in order to preserve the blood supply. A longitudinal incision was made in the tube down through the submucosa permitting the mucosa to pout out in a manner analogous to the pyloromyotomy of Fredet-Ramstedt. This incision equaled the length of the arterial graft. The sides of the incision were undermined and the graft laid into the muscular-submucosal trough. Interrupted mattress sutures buried the graft in the tunnel; these sutures were placed so as to include all layers of the bowel wall external to the mucosa (Fig. 1). In several animals the tube was opened and an inlay graft inserted intraluminally as a new lining. The distal end of the graft, which was to serve as the ostium, was either cuffed back on the amputated tube or fishmouthed and sutured to the serosa of the intact tube. The polyethylene strut was withdrawn in 6 animals, and maintained subcutaneously in the remaining 3. The contralateral tube was either reconstructed in a similar manner or amputated. We elected amputation of the contralateral tube in order to avoid confusing results in evaluating postoperative tubal insufflation, hysterosalpingography, and the results of spontaneous cohabitation.

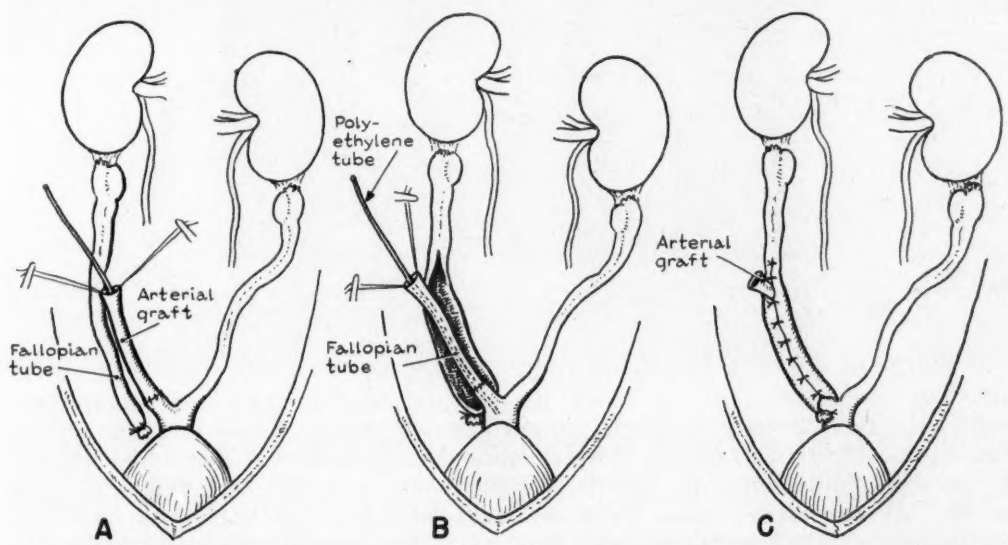


Fig. 1.—*A*, The uterine anastomosis has been completed and the graft is aligned in relation to the tube.

B, An inlay method of tubal implantation is used in this instance.

C, The graft is buried in the tubal wall and the ostial end is to be cuffed back. The contralateral tube is similarly reconstructed or removed.

Results

One animal died on the second postoperative day of pneumonia and a second of a purulent peritonitis eight days following repeated attempts at

*Supplied by the Ethicon Suture Laboratories, Inc., New Brunswick, N. J.

hysterosalpingography from below. The remaining 7 animals made an uneventful postoperative recovery. We made several attempts at hysterosalpingography but were not uniformly successful in introducing the dye beyond the cornu, even though subsequent studies showed patency of the area. Several trials with progesterone priming did not facilitate the procedure. After the death from peritonitis we preferred examining the grafts by a formal laparotomy. Our experiences with tubal insufflation were inconsistent, indefinite, and of unpredictable value in determining patency of the grafts. Exploratory operations were performed on the animals at intervals of 58 to 113 days, at which time gross inspection of the graft and patency determinations were made in situ. The genitals were completely removed for histologic studies of the buried graft.

Fig. 2.—Hysterosalpingogram demonstrating patency of the proximal anastomatic site and stricture of the body of the graft. There was no intraperitoneal spill.

The gross findings in regard to the ostium of the graft were uniform in all dogs examined. In all cases the ostium of the graft was completely occluded either directly or about the polyethylene tube. Small intestine, colon, and the posterior wall of the bladder were densely adherent about the ostium. In no case could fluid be injected from the uterus out into the peritoneal cavity. In the earlier cases the fluid could be forced to the ostium with distention of an otherwise patent graft conduit. The polyethylene strut maintained its own exit but not the ostium of the graft in relation to the free peritoneal cavity.

The utero-arterial junction was patent in all animals in the early series. Fig. 2 is a hysterosalpingogram done 85 days after reconstruction of the right tube, in which proximal patency of the graft and distal occlusion are well demonstrated. The remainder of the graft exhibited marked narrowing and shrinkage but maintained the gross morphologic appearance of an artery for periods up to ninety days. Histologic sections of these early grafts showed

complete lack of reaction between the blood vessel wall and the tube. There was no proliferation of endometrium along the graft and the intima of the artery was for the most part no longer discernible. The muscle cells of the media were replaced by fibrous tissue and there was fragmentation and reduplication of the elastic tissue (Fig. 3).

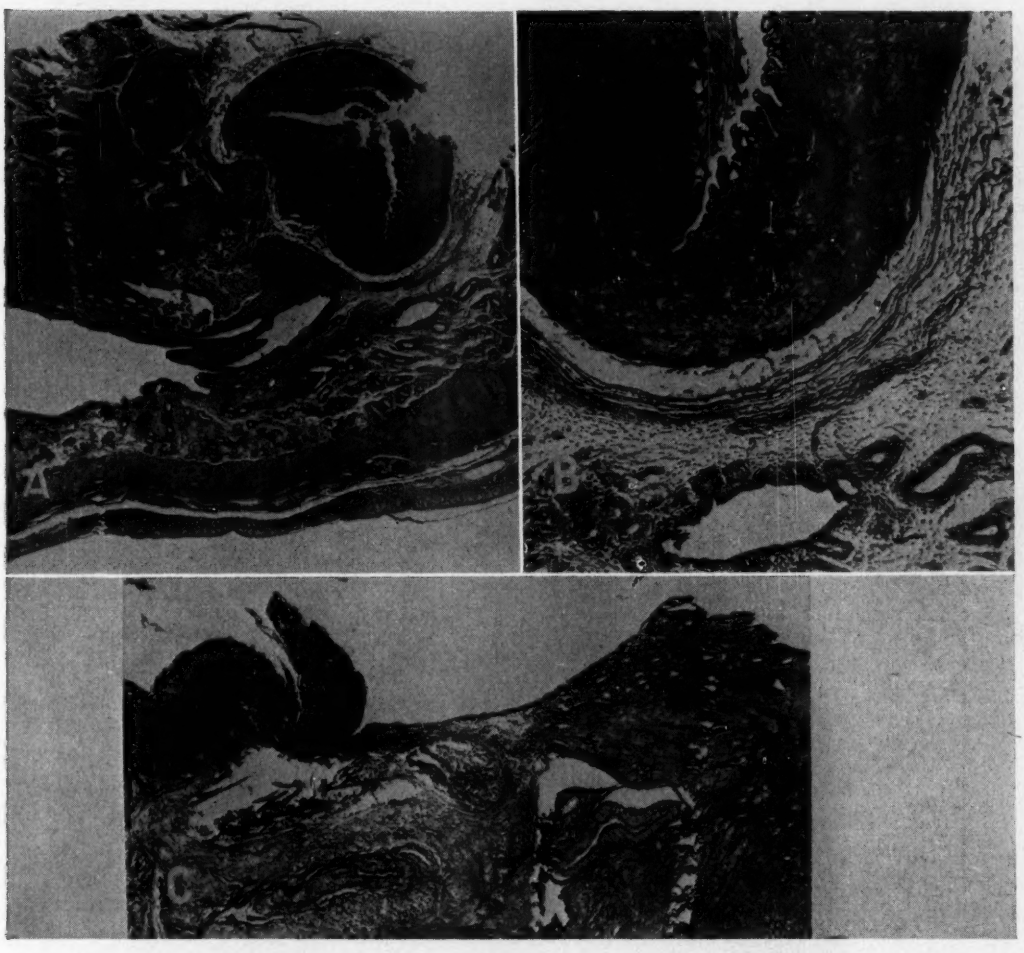


Fig. 3.—*A*, Photomicrograph demonstrating the general alignment of the graft in relation to the tunnel created within the wall of the tube. (×31.)

B, Higher-powered view of *A* at 58 days, demonstrating preservation of the lumen. The elastic coat exhibits moderate fragmentation and the muscle cells of the media are replaced by fibrous tissue. There is no reaction between the host tissue and the graft. (×90.)

C, The site of utero-arterial anastomosis exhibits no endometrial proliferation along the graft. There is no stricture at the site of the anastomosis. (×54.)

Two animals operated upon 96 and 113 days after tubal reconstruction are considered as the late results. Here again the ostium was completely occluded by surrounding organs. The graft was no longer recognizable except as a fibrous cord. Histologic sections through the graft and the host revealed no change in the tube, but there was complete dissolution and lymphocytic infiltration of all layers of the arterial wall with total loss of vascular integrity and conduit capacity (Fig. 4).

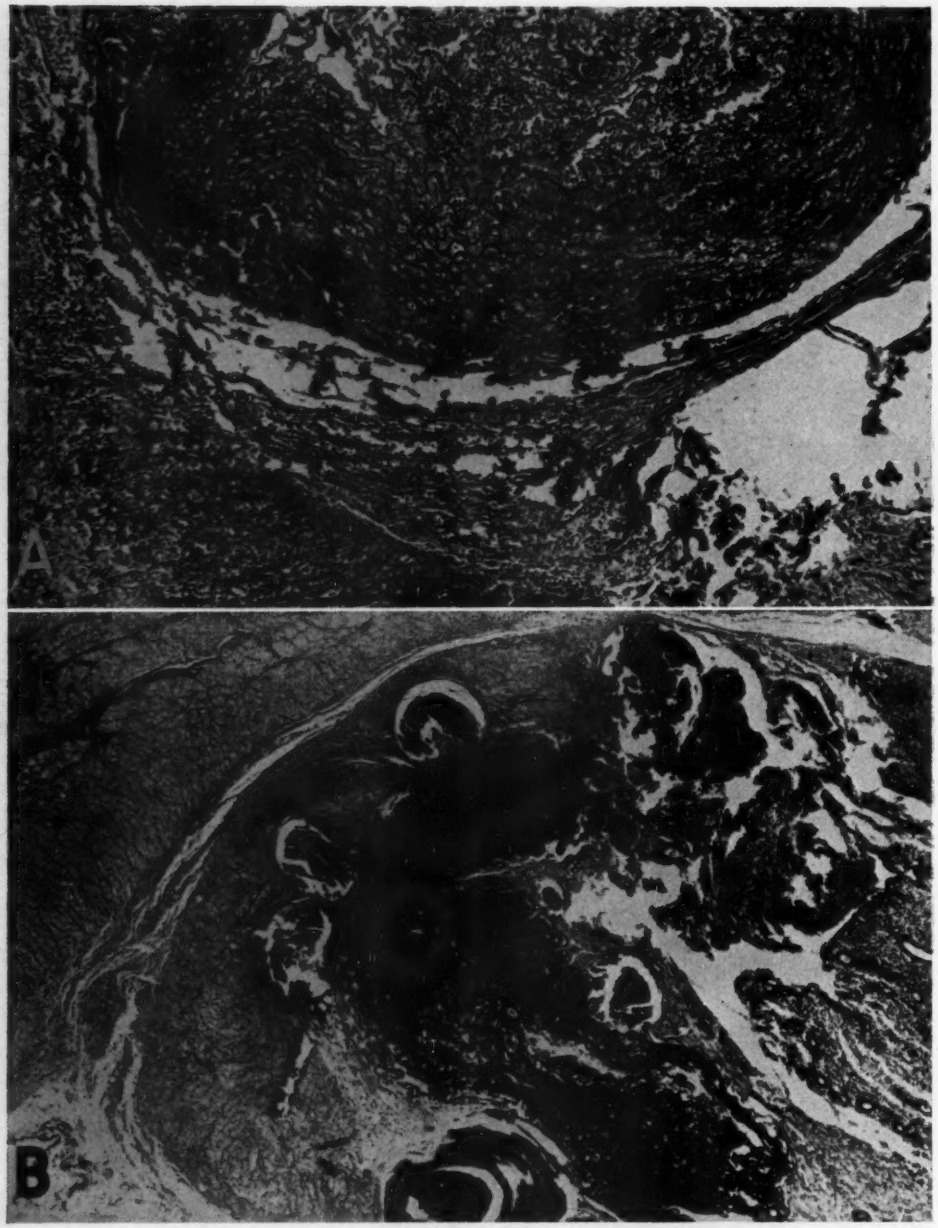


Fig. 4.—*A*, At 96 days there is beginning dissolution of the graft with round-cell infiltration into all layers. (×90.)
B, At 113 days the graft has completely degenerated. (×90.)

Comment

Previous experiences using the principle of the tunneled autogenous arterial graft to convey urine and bile indicated that the ultimate fate of the artery was not influenced by external vascularization when used to convey fluids other than blood. The behavior of an artery buried in the submucosa of the genital tube parallels this previous experience as regards ultimate de-

generation of the entire graft. There was, however, no replacement of the intima by host epithelium as had been demonstrated in the ureteral tract. In no case did the endometrium proliferate beyond the utero-arterial anastomosis onto the graft, regardless of whether or not a strut was employed. Castallo[2] has observed rechannelization of sectioned tubes in the monkey where the ends were bridged by a polyethylene strut. Such proliferation along the intima of the graft would provide a lubricated and familiar environment to the ovum. Even if the problem of closure of the ostium and periostial adhesions could be solved by intubation or the use of allantoic membranes,[3] and even if the lumen could be maintained by Gelfoam, paraffin, or a strut, the degeneration of the graft after ninety days interdicts the practical use of an artery for the reconstruction of the Fallopian tube. Davids and Bellwin[4] reported on the use of artery and vein as a complete substitute for the tube. In this experimental report no attempt was made to contribute an extravascular blood supply or peristaltic mechanism to the graft. From this preliminary report, based on a seven-week follow-up, the procedure appeared to be practical. Experience over longer periods of time has proved it to be disappointing and impractical.

Summary

1. Autogenous arterial grafts buried in submucosal tunnels were used to reconstruct Fallopian tubes in dogs.

2. In all cases the ostial end of the graft was occluded from the free peritoneal cavity by extensive peritubal adhesions.

3. The gross morphologic and conduit features of the graft at the cornu were maintained for periods up to 90 days.

4. After 90 days the graft degenerated and was converted into a fibrous cord.

5. The use of autogenous arterial grafts for the reconstruction of Fallopian tubes is not practical.

References

1. Bohm, E., and Englund S.: Acta obst. et gynec. scandinav. 26: 329, 1946.
2. Castallo, M. A.: Fertil. & Steril. 1: 435, 1950.
3. Castallo, M. A., and Wainer, A. S.: Am. J. Obst. & Gynec. 66: 385, 1953.
4. Davids, A. M., and Bellwin, A.: Fertil. & Steril. 5: 325, 1954.
5. Greenhill, J. P.: Am. J. Obst. & Gynec. 33: 39, 1937.
6. Hurwitt, E. J., and Kantrowitz, A.: Surgery 32: 76, 1952.
7. Israel, S. L.: Fertil. & Steril. 2: 505, 1951.
8. Lorset, J.: Acta obst. et gynec. scandinav. 20: 344, 1940.
9. Rubin, I. C.: Uterotubal Insufflation, St. Louis, 1947, The C. V. Mosby Company.
10. Solomons, B.: J. Obst. & Gynaec. Brit. Emp. 43: 619, 1936.
11. Sanders, A. R., Schein, C. J., and Hurwitt, E. S.: The Bridging of Long Ureteral Defects by Fresh Autogenous Grafts Embedded in Submucosal Intestinal Tunnels: An Experimental Study. Brit. J. Urol. (In press.)
12. Schein, C. J., Sanders, A. R., and Hurwitt, E. S.: The Fate of Fresh Autogenous Arterial Grafts Embedded in Submucosal Intestinal Tunnels as Applied to the Bridging of Ureteral Defects. Presented in part at the Surgical Forum, 40th Annual Clinical Congress, American College of Surgeons, Atlantic City, N. J., Nov. 15, 1954.
13. Schein, C. J., Hurwitt, E. S., and Ferreira, R.: The Use of Fresh Autogenous Arterial Grafts for the Experimental Reconstruction of the Common Bile Duct. (In preparation.)

ARTIFICIAL INSEMINATION

ROLAND BIEREN, M.D., WASHINGTON, D. C.

(From The Group Health Association)

IN AN eight-year period, 568 couples with an infertility problem have sought advice. Forty-four of these have requested artificial insemination as indicated in Tables I-IV. On an average, each woman was inseminated three times each menstrual cycle during the approximate fertile period. Semen is collected by masturbation into an open-mouthed 2 ounce ointment jar. Such jars are inexpensive and can be autoclaved. No lubricant is used; most women have sufficient vaginal secretion to allow the insertion of a speculum without discomfort. A sterile 10 ml. syringe and a sterile Rubin cannula are flushed with sterile saline; the semen is drawn into the syringe which is reattached to the cannula. Pressure is made on the barrel to bring the semen to the tip of the cannula which is then introduced to the level of the internal os and 0.3 ml. of semen is injected. The cannula is then withdrawn to a position halfway between the internal and external os and another 0.3 ml. of semen is injected. Finally, the cannula is withdrawn to the external os and the remaining semen is injected. Pressure is released between injections and no more than 0.3 ml. is injected at one time. This technique was used in 33 women who were inseminated with the husband's semen for a total of 298 menstrual cycles. Eight pregnancies and 8 living children resulted.

TABLE I. DONOR INSEMNATION

CASE NO.	CYCLES Rx	RESULT	SEMEN	AFTER Rx ENDED
1	4	Stillborn	Azo.	Adopted
2	1	Child	Sub.	
	7	Abortion		0
3	7	0	Azo.	Adopted
4	3	Child	Azo.	
	7	0		0
5	17	Child	Azo.	
	5	Abortion		
	7	0		0
6	8	0	Azo.	0
7	6	0	Azo.	Adopted
8	7	0	Sub.	
	*3	Child		
	2	Child		0
9	11	0	Azo.	Adopted
10	10	0	Azo.	Adopted
11	37	Abortion	Azo.	Adopted

*Changed to another physician after treatment for seven cycles was unsuccessful.

TABLE II. HUSBAND INSEMINATION: TUBAL OCCLUSION

CASE NO.	CYCLES Rx	RESULT	SEMEN	AFTER Rx ENDED
1	5	Child	Sub.	0
2	16	0	Sub.	0
3	11	0	Normal	0
4	6	0	Normal	0
5	8	0	Normal	Child
6	11	0	Sub.	0

TABLE III. HUSBAND INSEMINATION: NORMAL SEMEN; NO OCCLUSION

CASE NO.	CYCLES Rx	RESULT	AFTER Rx ENDED
1	11	0	0
2	8	0	0
3	3	Child	0
4	4	Child	0
5	6	0	Adopted
6	4	Child	0
7	8	0	Adopted
8	10	0	0
9	4	0	0
10	16	0	0
11	7	0	0

TABLE IV. HUSBAND INSEMINATION: SUBFERTILE SEMEN; NO OCCLUSION

CASE NO.	CYCLES Rx	RESULT	AFTER Rx ENDED
1	20	0	0
2	9	0	Adopted
3	7	0	Child
4	6	0	Adopted
5	7	0	0
6	6	0	Adopted
7	14	0	0
8	18	0	Adopted
9	5	Child	0
10	7	0	0
11	12	Child	0
12	6	0	0
13	18	0	0
14	12	0	0
15	8	Child	0
16	6	Child	0

An additional 11 women were referred to other physicians for insemination with a donor's semen for a total of 142 cycles. There were eight pregnancies in this group with 4 living children, one stillbirth, and 3 spontaneous abortions as the final result.

Eleven couples who failed to achieve a living child subsequently adopted children as indicated in the tables. Two couples had normal pregnancies several months after all treatment had been discontinued. Semen was classed as subfertile when counts were repeatedly less than 55 million with motility less than 50 per cent and an appreciable number of abnormally formed spermatozoa were present. In all cases labeled azoospermic, the diagnosis was confirmed by testicular biopsy.

Conclusions

1. It is possible that insemination with the husband's semen helped conception occur in the 8 successful instances reported.

2. When started, husband insemination should be continued for twelve menstrual cycles.

3. Donor insemination should never be recommended. When a couple insist upon such a treatment, they may be referred to physicians who are known to provide such a service.

4. By the law of averages, some women will have Mongoloids by donor insemination. In the series of 11 cases treated by donor insemination here reported, one stillborn child and 3 spontaneous abortions resulted.

Department of Case Reports New Instruments, Etc.

FIBRINOGENOPENIA IN A FIVE MONTHS' GESTATION

EDWARD C. VEPROVSKY, M.D., F.A.C.S., AND ALFRED C. LEVIN, M.D.,
FOREST HILLS, N. Y.

(From the Department of Obstetrics and Gynecology, Queens General Hospital, Jamaica, New York)

FIBRINOGENOPENIA in pregnancy has been observed in various pathological states. These include fetal death in Rh incompatibility, premature separation of the normally implanted placenta, toxemia, and amniotic fluid infusion—all associated with a hemorrhagic diathesis due to fibrinogenopenia.[1-4]

The patient presented in this report had an intrauterine gestation of 22 weeks, premature separation of the placenta, and fetal death with a hemorrhagic diathesis due to fibrinogenopenia. A review of the literature fails to reveal a similar case at such an early gestational age. The duration of the pregnancy, the similarity to numerous more or less routine admissions in all the various stages and forms of abortion, and the method of management under prevailing circumstances prompted the report of this case.

Case Report

Y. B., No. A28602, a 26-year-old Negro woman was admitted on June 14, 1954, with a chief complaint of profuse vaginal bleeding which had begun suddenly two hours prior to admission. For several hours before the onset of bleeding the patient complained of severe, irregular abdominal cramps with increasing pain and tenderness of the hypogastrium. The last menstrual period was Jan. 7, 1954, and the estimated date of confinement Oct. 14, 1954. She was type O, Rh negative, with a negative serologic test, para ii, and gravida iv. She had had two normal spontaneous deliveries at term, and the last pregnancy had terminated in a spontaneous abortion at ten weeks of gestation. There was no other contributory medical or surgical history.

The blood pressure was 120/80, pulse 110, temperature 99° F. Scant bleeding was noted from the mucous membranes of the nose and mouth. The fundus was of approximately the size of a five months' gestation, the left upper pole exquisitely tender to palpation. There were irregular uterine contractions of poor quality with constant pain in the left upper portion. The fetal heartbeat was not audible nor was there any history of fetal movement. The vaginal bleeding was constant, profuse, and showed no signs of a gross clot. The membranes had been ruptured for two hours; the cervix was softened and dilated 2 cm. Gross hematuria was found on catheterization.

Blood drawn for typing and cross-matching showed no evidence of a gross clot after ninety minutes. A quantitative plasma fibrinogen determination after the method of

Schneider[5]* showed no clot in any dilution. The blood sample drawn at this time later showed a fibrinogen level of 78 mg. per cent. An infusion of Pitocin, 1:1,000, was begun intravenously and 500 c.c. of fresh blood was given. At the end of two hours there was no appreciable change in the status of the cervix or in descent of the presenting part. The patient's general condition remained unchanged with the bleeding constant although not as profuse as on admission. The blood pressure was 120/80, pulse 100. Another 500 c.c. of fresh blood was given and the "Schneider test" performed with no clot visible in any dilution.

Under these circumstances it was apparent to us that vaginal delivery was not feasible. Immediate hysterotomy was performed under cyclopropane anesthesia. Four grams of fibrinogen was given at the time of the abdominal incision. The uterine cavity was emptied of approximately 600 c.c. of frank blood characterized by friable, unstable clots. The macerated, stillborn fetus was 23 cm. in length. The placenta was almost entirely separated from the uterine wall. Vaginal bleeding stopped immediately after the operation and there was no evidence of further bleeding from the nose or mouth. The Lee-White clotting time was ten minutes, the Schneider test performed showed a stable clot at a titer of 1:100.

The first postoperative day was marked by a gross hematuria in a total urinary output of 500 c.c. Twelve hours postoperatively the clotting time was three minutes, and a stable clot was noted in the Schneider test in a dilution of 1:400. The quantitative fibrinogen determination was 378 mg. per cent. The patient was observed cautiously and medical consultation was obtained. Fluid intake was limited to approximately 1,000 c.c. plus the equivalent urinary output. Blood chemistry values were all within normal limits. On the second postoperative day the urinary output rose to 800 c.c. with only occasional red blood cells per microscopic field. On the third day the urinary output was 1,400 c.c. Urine and blood chemistry values were all within normal limits with the exception of the blood urea nitrogen and creatinine which rose to levels of 46 mg. per cent and 9 mg. per cent, respectively, in spite of adequate fluid intake and output. After the sixth day the blood chemistry values gradually returned to normal. Prophylactic antibiotics were given and there were no significant temperature elevations after the second postoperative day. Convalescence was otherwise uneventful and the patient was discharged to the outpatient department on the sixteenth hospital day. Subsequent clinical and laboratory evaluation three months postoperatively disclosed no abnormalities.

Summary

1. A case of fibrinogenopenia in a five months' gestation is reported.

2. The diagnostic technique and management are presented.

3. An example of the use of the Schneider test as a simple, rapid means of estimating plasma fibrinogen is given.

Conclusion

In all too many instances, adequate laboratory facilities are not available for accurate, emergency fibrinogen determinations. The need for maintaining

*A rapid assay method of estimating plasma fibrinogen levels was outlined several years ago by Dr. Charles L. Schneider. Recently, there has been an increasing awareness of the need for such a procedure. Subsequent clinical trial of the method has led, appropriately, to general recognition of the procedure as the "Schneider test."

The technique of the test is simple and it is readily performed with standard ward equipment. Approximation of fibrinogen is obtained in terms of a titer. It is assumed that the average hematocrit is 35. Venous blood is mixed with Ringer's lactate solution in eight serially diluted test tubes in a dilution range of 1:10 to 1:1,600. These are read after being mixed and allowed to stand at room temperature for one hour. The titer is read as the highest dilution in which there is a visible clot. This is an approximate estimation of plasma fibrinogen in milligrams per cent. The trend toward the critical level of 100 mg. per cent is readily demonstrated.

The value of the determination is further emphasized by the fact that normal clotting times have been obtained in the presence of fibrinogen levels as low as 60 mg. per cent.

fresh, adequate fibrinogen stocks in all hospitals must be emphasized. This case also emphasizes the necessity for appropriate action to eliminate the cause of the fibrinogenopenia concomitant with the administration of fibrinogen. The routine performance of Schneider tests and clotting time determinations should not be restricted to occasional cases of third-trimester bleeding, but of necessity the indications for the routine use of these tests should be extended to include all instances of vaginal bleeding at any gestational age where early diagnosis and proper therapy may well avert catastrophe.

References

1. Dieckmann, W. J.: AM. J. OBST. & GYNEC. 31: 734, 1936.
2. Seegers, W. H., and Schneider, C. L.: Trans. Internat. & Fourth Am. Congress on Obst. & Gynec. (supp. vol. Am. J. Obst. & Gynec.) 61A: 469, 1951.
3. Weiner, A. E., Reid, Duncan E., and Roby, C.: AM. J. OBST. & GYNEC. 60: 379, 1950.
4. Reid, Duncan E., Weiner, A. E., Roby, C., and Diamond, L.: AM. J. OBST. & GYNEC. 66: 500, 1953.
5. Schneider, C. L.: AM. J. OBST. & GYNEC. 64: 141, 1952.

DEATH DUE TO THE INITIAL HEMORRHAGE IN PLACENTA PREVIA WITHOUT MANIPULATION

LOUIS ROSNER, M.D., HOUSTON, TEXAS

(From the Department of Obstetrics and Gynecology, Baylor University College of Medicine)

HERMAN JOHNSON in 1950 stated that he had never seen or heard of a fatality from the initial bleeding of placenta previa, in the absence of digital manipulation of the cervix.

The history of this case was obtained from the husband, mother, and sister-in-law of the patient, and from the midwife.

M. O. was a 39-year-old gravida vii, para iv. She was at term in September, 1954. She went to a midwife once a month for prenatal care. She had no bleeding during the entire nine months until the onset of the terminal hemorrhage. The only complication of the pregnancy was "hurting in the stomach" which persisted for the last two months.

The last visit to the midwife was on the night of October 6 when nothing unusual was noted. Blood pressure was taken, weight measured, and the abdomen palpated.

On the night of October 7 she complained of pains in the pelvic region, swollen feet, and cold thighs.

On October 8, at 1:30 P.M., she began to have intermittent pains and to bleed profusely from the vagina. She lay down in bed with the feet raised. The midwife was called by the sister-in-law but could not be reached at first. Meanwhile, she continued to bleed; and a small tub able to hold about a gallon of fluid was more than filled with blood, clots, and pads—and yet she bled more. A rag was tied around the abdomen as an abdominal binder.

The midwife arrived a little before 2:00 P.M. She examined the sides of the abdomen by palpation and felt the baby kick. The sister-in-law, who was with the patient the entire time, testified that the midwife did no vaginal examination of any type. Because of the importance of proving the lack of any manipulation, it is well to emphasize this point. The history here is reliable. The family was not trying to protect the midwife, but rather was very vehement in denunciation of her, placing much of the blame for the patient's death on the failure of the midwife to do anything. Thus, the sister-in-law, having been with the patient from the beginning, was able to certify that absolutely no digital manipulation was done.

On seeing the bleeding, the midwife took the patient's legs down from the stool on which they were propped and recommended calling a doctor (telling the patient at the time that the bleeding was due to "too much alcohol in the veins"). She was with the patient no more than 10 minutes.

The ambulance arrived at 2:05 P.M. Meantime, the patient had cold sweats and vomited twice (only food, no blood): once at home and once in the ambulance. She arrived at St. Joseph's hospital at 2:30 P.M.

Dr. V., a general practitioner, had been called by the family. When the patient arrived at the emergency room, the nurse immediately informed Dr. B., who told the nurse to put her on the table for examination. However, when the nurse saw the pool of blood with the huge clots, she sent her immediately to the delivery floor.

She was admitted to the delivery floor at 2:50 P.M. She was still bleeding profusely; there were about 2,000 c.c. of blood on the bed and numerous large blood clots. The blood pressure could not be heard at this time.

After 3 to 4 minutes, she was taken to the delivery room and put on the table. At this time the patient became irrational and began to thrash around wildly, evidently because of air hunger. She was in deep shock, with cold, clammy skin; conscious, but not rational; and there was a mild trickling of dark blood from the vagina and dark clots in the introitus. She had a pregnant term-size uterus, which was relaxed.

The patient was put in Trendelenburg position, covered with a blanket, and the legs put up in stirrups (but shortly taken down). One-thousand cubic centimeters of 5 per cent glucose was started intravenously (approximately 7 to 8 minutes after arrival on the floor) first in the left arm, knocked out by the patient, then in the right arm. Fifty milligrams of Demerol and 0.2 mg. hyoscine were given to control violent movements. Five hundred cubic centimeters of Type O, Rh-Negative blood was started in the right arm (approximately 15 minutes after the patient was brought to the floor). There was difficulty in giving blood because of her violent movements. The blood was dripped at first and then pumped. An attempt was also made to start a transfusion in the left arm, and a cut-down was begun on the right leg. At this time there was a faint pulse; fetal heart tones were not heard; the blood pressure was not heard by the anesthetist, but was obtained at 45 systolic by the resident at one time before the blood was started, but none after.

The patient died at 3:30 P.M., before more than 250 c.c. of blood could be given. This was two hours after the onset of bleeding and 40 minutes after she was brought to the floor.

Immediately after death, a vaginal examination was performed for the first time, and the cervix was found to be 50 per cent effaced, 5 to 6 cm. dilated, with a central placenta previa.

A cesarean section was done which confirmed the total placenta previa, though this was left undisturbed.

The clinical impression at death was: (1) central placenta previa with fatal hemorrhage; (2) intrapartum fetal death in utero plus erythroblastosis fetalis.

Autopsy.—An autopsy was performed four hours after death and revealed the following:

A normally developed, fairly well-nourished young woman (148 cm. from crown to heel) with a female fetus that weighed 4,445 grams and was 54 cm. long. The fetus had an enlarged hyperemic liver and subserosal petechiae in heart, lungs, thymus. The mother had marked pallor of the liver. Placenta previa centralis: normal in size and shape, hemorrhagic discoloration of maternal surface, placental tissue easily separated from myometrium. Uterus: 10 cm. incision in lower anterior wall, no tears or lacerations in cervix or uterine wall. Brain: congestion over convexities of hemispheres.

The microscopic findings were as follows: Lungs: foci of emphysema alternating with areas of atelectasis; moderate dilatation of small vessels. Uterus: hypertrophy of fibers of myometrium (as seen in pregnancy) and attached placental tissue separated from myometrium by zone of decidual tissue. Anterior pituitary: large cells with partly vacuolated cytoplasm (pregnancy cells). Fetus: (A) Lungs: majority of the alveolar lumina expanded slightly, containing elements of amniotic fluid and blood. (B) Liver: a few minute foci of extramedullary hemopoiesis seen, but not exceeding the usual findings noted in newborn infants.

Comment.—"Determination of the cause of the maternal death in the present case depends mainly on a process of elimination. Grossly, there was a suggestion of acute anemia in view of the pallor of the organs, particularly noticeable in the liver. A considerable number of microscopic sections were studied; especially numerous were the sections from the lungs, the central nervous system, and the uterus. No evidence of amniotic fluid embolism is demonstrated nor do any of the sections reveal disseminated fibrin emboli. The possibility of eclampsia or pre-eclampsia is ruled out by the essentially normal appearance of the sections from the liver and the kidneys. There is, therefore, no anatomically demonstrable lesion that would explain the patient's death. The acute blood loss appears as the most plausible cause, although some other remote possibilities, such as shock due to sensi-

tivity to some protein or drug, cannot be ruled out, since they have no specific anatomical lesion. The gross and microscopic examination of the placenta and fetus fails to reveal any evidence of erythroblastosis fetalis. There were, in particular, no signs of hydrops. The presence of a zone of decidua between the myometrium and the chorionic villi speaks against the possibility of placenta accreta, and it seems, therefore, that the only demonstrable cause of the hemorrhage lies in the previa type of placental attachment.''

Anatomical Diagnosis.—Findings compatible with acute anemia due to hemorrhage. Placenta previa centralis. (Dr. Peter Marcuse, Pathologist.)

Conclusion

This represents a case of total placenta previa (proved at postmortem cesarean section and at autopsy), the patient dying from the initial hemorrhage without manipulation. No other cause of death could be found at autopsy. Thus is proved again the old maxim that there is no such thing in medicine as ''never'' or ''always.''

Note by Dr. Herman W. Johnson

The exception to a rule proves the rule. This case report appears to fulfill all the conditions stipulated in my paper which appeared in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, Vol. 59, Page 1236.

I feel that I have accomplished much in the way of removing the goblins about placenta previa which appeared in the acceptable textbooks prior to the last decade.

Since my paper of 1945, there have been approximately 31,193,907 births in the United States. If the cases of placenta previa average 1.7 per cent of total births (combined average of leading maternity hospitals of the United States), then there would have been 530,296 cases of placenta previa. I feel that no physician should become unduly alarmed at the prospect of his patient bleeding to death with the initial hemorrhage.

Your case has been the first to present a claim for the award under the conditions which I stipulated.

HERMAN W. JOHNSON, M.D.
Chairman of the Department of Obstetrics and Gynecology

CERVICAL MYOMA SIMULATING AN ECTOPIC PREGNANCY

E. C. Sites, M.D., F.A.C.S., F.I.C.S., J. J. Coury, M.D., and J. A. Barss, M.D.,
Port Huron, Mich.

(From the Port Huron Hospital)

THE location and shape of this cervical myoma and the symptoms presented a clinical picture of an ectopic pregnancy. It was impossible to rule out a cervical myoma without a pneumoperitoneum.

Case Report

This 48-year-old white woman was admitted to the Port Huron Hospital with the chief complaint of abdominal pain and vaginal bleeding associated with an intestinal upset. The patient had regular menstrual periods of a 26 day type except for the last period which was scanty and of a shorter duration. The last menstrual period was February 4. Three days prior to admission the patient had a diarrhea which was not associated with an elevated temperature. She had several episodes of vomiting. One day prior to admission to the hospital she had a dark vaginal discharge with bright red bleeding. This occurred 14 days after the last menses.

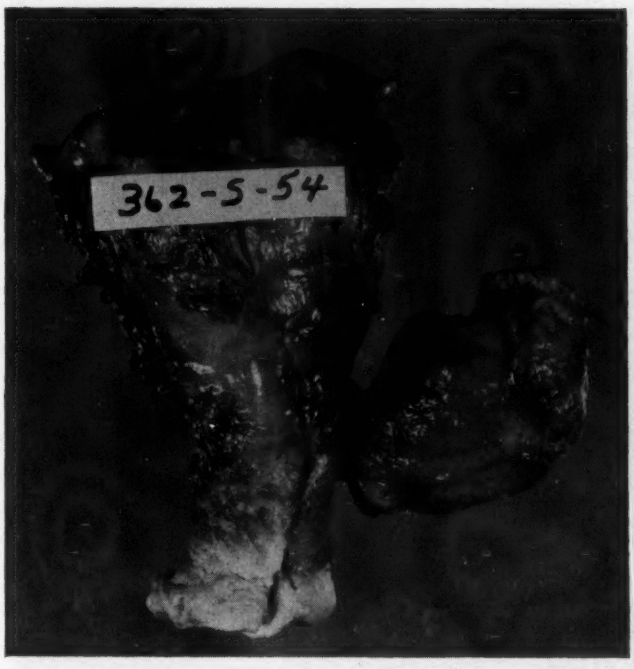


Fig. 1.

On admission the temperature was 98.8° F., and the blood pressure was 140/90. Marked tenderness was present in the right lower quadrant. Pelvic examination showed the vagina to be full of dark and bright red blood. The uterus was approximately of normal size. In the right adnexa there was a 3 cm. rather irregular tender mass, which

seemed to move with the uterus. The left adnexa were normal. A presumptive diagnosis of right estopic pregnancy was made. The laboratory reports showed a trace of albumin; erythrocyte count 4.3 million; leukocyte count 5,500; hemoglobin 12.5 Gm. per 100 ml.; total polymorphonuclear leukocytes 79, of which 14 were stab cells and 65 segmented cells, 20 lymphocytes, and 1 eosinophil. The frog pregnancy test was reported negative.

Prior to operation, the patient was re-examined under anesthesia and a right adnexal mass as previously described was found but it was impossible to outline or determine the exact character of this mass. At operation the abdominal viscera were explored and were found to be negative. There were a myoma on the anterior surface of the uterus and a mass extending into the broad ligament above the uterosacral ligament. This mass was firm and adherent, and a diagnosis of a cervical adenomyoma was made at this stage of the operation. In view of the presence of another myoma a hysterectomy was performed. The patient had a normal postoperative course and was discharged on the ninth postoperative day. Fig. 1 illustrates the right adnexal mass.

Pathological Report.—The specimen consisted of a total uterus with an intraligamentary pedunculated cervical myoma 3.5 cm. above the external os and a myoma on the anterior surface of the uterus. The attached pedunculated myoma measured 4 by 2.5 cm. and had a dark congested bluish-white color. Microscopic sections of the tumor showed a fibromyoma.

Summary

A case is reported of an intraligamentary cervical myoma which, on account of its location, contour, and the physical findings, made it difficult to rule out an ectopic pregnancy.

301 Michigan National Bank Building
802 Military Street

FETUS COMPRESSUS

A Case Report

DAVID K. MULLIKEN, M.D., HUDSON, N. Y.

(From the Department of Obstetrics and Gynecology, Rip Van Winkle Clinic)

THE unforeseen appearance of a small macerated or mummified fetus following the normal delivery of a full-term viable infant has been reported as a startling phenomenon by various authors beginning centuries ago. The comprehensive study by Kindred in 1944 noted 150 cases recorded at that time. There have since been added at least three more.

Mrs. L. C., a 41-year-old gravida vii, para vi, was admitted to the Columbia Memorial Hospital on Sept. 8, 1954, in early labor. Her menstrual history was somewhat uncertain, but her estimated date of confinement was early September.

Fig. 1.—Placenta and fetus showing maceration and compression of fetus as well as difference in the two portions of the placenta.

She had had six full-term pregnancies, all essentially uneventful and all terminating in single live births. Her present pregnancy had been similarly uneventful save for one day of vaginal spotting, which she was certain occurred about one month following her last regular period. She had been first seen for antepartum care on May 8, 1954, at which time the uterus was enlarged to a point just below the umbilicus. The remainder of the

physical examination was unremarkable. The urine was normal, hemoglobin 11.2 Gm., per 100 ml. and the serologic test was negative. The pregnancy progressed apparently normally with an average-sized fetus presenting by the vertex, but with possibly some increased amount of amniotic fluid.

Following admission to the hospital her labor accelerated, and at 4:30 A.M. she was delivered of a 6 pound 8 ounce male child. The child cried spontaneously and was apparently in good condition. The placenta separated promptly and on its appearance at the introitus it was noted that one-half of its total area appeared to be completely infarcted, white and fibrous. The placenta was followed immediately by a yellow-gray necrotic membranous sac containing a small amount of thick fluid and a flattened, macerated fetus of about 4 months' gestation. The fetal parts were easily identifiable, although grossly deformed and compressed.

The pathological report was: the specimen consisted of a twin placenta. One portion measured 15 cm. in diameter and had normal cotyledons and a centrally placed cord. The other portion measured 11 by 7 and was white, hard, and fibrous throughout. There were two amniotic cavities and the two portions were sharply demarcated from each other. The cord of the infarcted placenta was macerated and there was attached a macerated fetus 25 cm. in length (Fig. 1.).

Diagnosis: Uniovular placenta with infarct of one half and macerated fetus (20 weeks).

Comment

A case of fetus compressus is presented, which was unsuspected until delivery and exhibited many of the most common findings in the 150 cases summarized by Kindred. The uneventful course of the pregnancy which he noted "is the rule rather than the exception," the mild degree of hydramnios, the timing of the delivery, and the appearance and state of preservation of the blighted fetus all are typical of this rare entity.

References

1. Kindred, J. E.: Am. J. Obst. & Gynec. 48: 642, 1944.
2. Posner, A. C., and Klein, M. A.: Obst. & Gynec. 3: 106, 1954.
3. Arends, N. W., Otterbein, D., Thornton, W. H., and Kester, G. E.: J. Am. Osteo. A. 50: 611, 1951.
4. Sabath, D. J., Kvitek, L. C., and Baugher, A. H.: Am. J. Obst. & Gynec. 56: 989, 1948.

OCCLUSIVE TRACHELORRHAPHY FOR REPEATED ABORTION DUE TO CERVICAL INCOMPETENCE

HERBERT H. HALL, M.D., NEW YORK, N. Y.

IN RECENT literature the importance of sphincter action of the internal os during pregnancy has been stressed. Danforth, discussing the paper of Rubovits, Cooperman, and Lash, objected to the contention that incompetency of the internal os alone was responsible for abortion. He suggested that the whole structure of the cervix itself might be involved. This view finds support in the report by Fisher, who quotes a high abortion rate in women whose cervices had been amputated. This may possibly be caused by the inability of the amputated cervix to function properly as a sphincter to the uterine cavity during pregnancy. In the case here reported the patient had lost two consecutive pregnancies after a high amputation of the cervix.

Mrs. M. M., aged 36 years, blood type B, Rh positive, was seen first on June 18, 1953. She was then about five weeks pregnant and speculum examination showed the vaginal portion of the cervix to be absent. She stated that in 1949 she underwent a vaginal operation and inquiries made of her attending physician disclosed this to have been an amputation of the cervix for erosion and chronic inflammation. Her pregnancy continued uneventfully until the twenty-sixth week when the membranes ruptured. Ten days later she delivered a 2 pound male infant that did not survive delivery.

She conceived again four months later and was given supportive hormonal therapy. This pregnancy terminated at the twelfth week in abortion. At that time a complete absence of the cervix was noted and it was evident that the cervix must have been amputated at or above the level of the internal os. Only anteriorly was there a small lip of cervical tissue left. After her recovery from the miscarriage a hysterogram confirmed these findings. It was felt that the reason for her failure to carry her pregnancies was the absence of a competent cervix, so that, after the corpus uteri enlarged in pregnancy, the lower end of the cavity widened, as it would normally, and the contents virtually "dropped out of the uterus" due to the absence of the cervix. An attempt to reconstruct the internal os was considered technically impossible since there was no tissue available for this purpose. It was decided, therefore, to permit her to conceive again and to occlude the entrance to the uterus by suture as soon as possible after that event.

The patient became pregnant again, with the last menstrual period on Jan. 16, 1954. On Feb. 23, 1954, after a positive pregnancy test, she was admitted to the hospital. Under intravenous Pentothal anesthesia the vagina was exposed and the entrance to the uterine cavity was occluded by a mattress suture. Using Nylon filament, the suture was placed in such a fashion that it would encircle the opening of the uterus and two ¾ inch lengths of polyethylene tubing were used to prevent the suture from cutting through.

The patient had been receiving progesterone by injection for seven days preoperatively and this was continued for two weeks following the operation. After that time she received oral progesterone and stilbestrol in increasing dosage.

The further course of this pregnancy was uneventful, and there was no pain and no vaginal discharge or bleeding.

At the thirty-fourth week of pregnancy the patient had a severe bout of diarrhea and following that the membranes ruptured. Soon after this, uterine contractions set in and she was admitted to the hospital. At that time the contractions occurred regularly every five minutes. Vaginal examination showed the suture in its original position occluding the uterine cavity. Considerable thinning of the lower segment was noted. The suture was cut whereupon a dilatation of about 5 cm. was noted. Further dilatation followed rapidly and spontaneous delivery of a living female infant followed within 45 minutes. The baby weighed 5 pounds 4 ounces and was in good condition. She survived the neonatal period uneventfully.

Summary and Conclusion

1. A case of repeated miscarriage following a high amputation of the cervix is reported.

2. Support is given to the contention that amputation of the cervix has a high abortion rate in subsequent pregnancies.

3. An operative procedure for the management of such cases is described and further trial of this method is suggested.

References

Fisher, J. J.: AM. J. OBST. & GYNEC. 62: 644, 1951.
Lash, A. F., and Lash, S. R.: AM. J. OBST. & GYNEC. 59: 68, 1950.
Rubovits, F. E., Cooperman, N. R., and Lash, A. F.: AM. J. OBST. & GYNEC. 66: 269, 1953.

Department of Reviews and Abstracts

EDITED BY LOUIS M. HELLMAN, M.D., BROOKLYN, N. Y.

Review of New Books*

Urology, Volumes I, II, III. Edited by Meredith Campbell. 863 pages with 1148 illustrations. Philadelphia, 1954, W. B. Saunders Company. $20.00 per volume.

This collection of "Masterworks" dealing with the genitourinary tract is in three volumes. It differs from the usual textbook on urology in that it is not just a collection of material on each subject. Instead its chapters were written by 52 well-known authors, each a man or woman who had made a particular study of or had a particular interest in each subject. Huggins, for instance, wrote the chapter on physiology of the prostate, Hotchkiss on infertility, Hinman on urinary obstructions, Narath on the physiology of the renal pelvis, Dean on carcinoma, Millin on retropubic prostatectomy. Noted authors from other fields were borrowed freely: e.g., Engle and Jailer have written on endocrinology, Rovenstein on urological anesthesia, Wharton on urological gynecology. The relationship between gynecology and urology is extensively treated, so that this work might be of particular value to the gynecologist. At least one new and fundamental change in the treatment of cryptorchidism has been presented by Dr. Engle, who demonstrates that the testis should be brought down before the sixth year, rather than at puberty. In addition to the clinical chapters, there is some consideration of physiology, anatomy, biochemistry, and endocrinology as they apply to urology.

This assemblage of noted authors has been made possible by Dr. Campbell's personal acquaintance with the leaders in the field of urology. Many of the chapters are classical monographs. This enables the reader to restrict his attention to the most valuable single piece of work in each field, and saves him the trouble of searching the literature to weed out the material of lesser importance.

Not only are 51 urological topics covered by responsible authorities, but Dr. Campbell has recapitulated his own views in a 200 page chapter on pediatric urology, in the second of the three volumes.

This is not the ideal textbook for the beginning student or for the undergraduate student of urology in that it does not bother with concise presentations of the elementary matters of Urology. This book should, however, be in the library of every medical school, urological clinic, and urologist's office where classical urological works are continually sought out for reference.

Man's Capacity to Reproduce. By Joseph W. Eaton and Albert J. Mayer. 59 pages with 20 tables. Glencoe, Ill., 1954, The Free Press. $2.00.

This well-written and well-investigated work is a report of the "demography of a unique population," the Hutterites of North America. These people settled in southeastern South Dakota between 1874 and 1877. The facts that these people have migrated little, have kept accurate vital statistics concerning themselves, have used no birth control measures, and that reproduction has proceeded without conscious planning make them an ideal group for such a study. The investigators have carried out a detailed and accurate study. Their volume is filled with many interesting data. Unlike most such studies, this one is a pleasure to read.

This population has been increasing at a rate of 4.1265 per cent annually, i.e., they double their population every 16 years. Thus the authors predict with confidence that in

*The Advisory Committee on Policy has agreed that most book reviews need not be signed.

1960 there will be "12,700 Hutterites living in . . . 130 colonies." This is due to the fact that the Hutterite woman may expect to have 12 children.

Adult Hutterites live longer than other American whites, and the males outlive the females. They are a most fertile people; a woman living with her husband between the ages of 47 and 51 has 86 chances per 1,000 of becoming a mother.

With these few paraphrases the report is enthusiastically recommended to anyone who wishes to discover what will happen population-wise in "underdeveloped areas" which are now receiving much aid and enlightenment from the United States.

Textbook of Pediatrics. Edited by Waldo E. Nelson. Sixth edition. 1581 pages with 440 illustrations. Philadelphia, 1954, W. B. Saunders Company.

The current edition of this text is the last in the series started by Dr. Griffith in 1933, continued under the authorship of Griffith and Mitchell, then Mitchell and Nelson, and now edited by Dr. Nelson.

The volume is a complete textbook. The various sections have been written by an imposing list of experts in their various fields. The special section on "Poisoning From Drugs, Metals and Food" is especially valuable from a therapeutic standpoint. Drs. Harry Feldman and John Anderson have organized this particularly well.

The liberal use of color plates makes the volume of greater value to the student and practitioner. The editor and publisher are to be congratulated on a production which, while heavy, 1581 pages, is easy to read. The split page format and clear type are appealing in style and easy on the eyes.

Finally, the editor is to be congratulated on the degree to which his contributors have made their presentations current.

Problems of Infancy and Childhood. Edited by Milton J. E. Senn. 196 pages. Packanack Lake, New Jersey, 1954, Josiah Macy, Jr., Foundation. $2.75.

This volume is a report of the final Conference on Infancy and Childhood sponsored by the Josiah Macy, Jr., Foundation.

As was the case at the conferences which preceded the one here reported, the participants are experts in their particular fields of endeavor. The discussions at the "round table" are faithfully reported. These "free" discussions frequently lead the reader off the track of the main subject but by and large are rewarding. The informality of the discussions not infrequently encourages the exploration of tangents and temporary or permanent loss of the main theme.

The subjects covered in the seventh conference were:

1. Truisms in Child Rearing
2. Effects of Mother-Child Separation
3. Children in Israel
4. Tendencies in the Second Year of Life
5. Report of the Subcommittee on Rooming-in

One is happy to learn from the discussions that mothers, in general, are quite capable of dealing with the problems of Infancy and Childhood.

Dr. Fremont-Smith's introduction is concise and makes very clear the objectives of the type of conference sponsored by the Foundation.

Die Brustdrusenerkrankunger. By Josefine Stahl and Hans-Joachim Englert. 162 pages with 110 illustrations, Leipzig, 1954, Georg Thieme. DM 29.50.

This compact monograph discusses the development of the normal breast and its response to hormonal influences and then discusses benign and malignant breast disease. It is profusely illustrated with excellent photomicrographs and photographs of the gross appearance of various breast lesions, particularly carcinoma.

Surgical and radiological therapy of breast carcinoma is thoroughly detailed. There is a short section on the prognosis of mammary carcinoma. This is an excellent short monograph.

Current Therapy. Edited by Howard F. Conn. 692 pages. Philadelphia, 1955, W. B. Saunders Company.

This volume, edited by Howard F. Conn, is a compilation of the "latest approved methods of treatment for the practicing physician." There are 12 consulting editors and 287 contributors. The methods of therapy presented cover almost every aspect of medicine. The section on obstetrics and gynecology is well organized and up to date. It occupies 48 of the 692 pages of the book, which indicates to some extent the brevity necessary for a volume of this type.

Alternate methods of treatment are described.

This is a good, quick reference book for refreshing one's memory on the details of various treatment regimes.

Medical Progress, 1955. Edited by Morris Fishbein. 346 pages. New York, 1955, McGraw-Hill Book Company, Inc. $5.00.

The book gives the reader a comprehensive account of the latest advances in diagnosis and treatment in all the major medical specialties. It is edited by Dr. Fishbein and the individual chapters are written by recognized authorities in their respective fields. The material is well organized and ample references are provided. New therapeutic agents such as chlorpromazine and steroid hormones, as well as the newer antibiotics, are discussed in detail as far as their application in the various specialties is concerned. The book undoubtedly is a valuable addition to a physician's bookshelf.

Gynécologie. By Nicholas C. Louros. 404 pages with 397 illustrations. Paris, 1954, Expansion Scientifique Française.

This treatise on theoretical and practical gynecology is designed for the use both of medical students and of practicing physicians. It is a French translation from the original Greek of the Chairman of the Department of Obstetrics and Gynecology at the University of Athens. The emphasis and viewpoint presented in this work differ considerably from those which characterize American practice. Consequently, certain aspects of the work may strike the American reader as singular. For example, the discussion of the morphology and physiology of the female body is written from the point of view of ideal anthropologic measurements, an approach to which the American gynecologist is hardly accustomed. In the section on constitutional physiologic types of women, the author indulges in a rather high-flown philosophic discussion of male-female relationships, racial and basic drives, and the interrelationships between body type and intellectual capacity. There follows a succinct section on hormones, vitamins, and enzymes as they relate to the economy of the female body. The author discusses the physiology of coitus in an extensive and well-organized section, but an almost equal amount of space is devoted to the diagnosis of rape. The section on the menopause is short and inadequate. Female hygiene is much more elaborately covered than in most American works. In connection with the gynecologic examination, on the other hand, major emphasis is given to the deportment of the physician rather than to the actual technique of examination.

In the section on female pathology, two general parts precede the discussion of diseases of the female genital organs. These deal, respectively, with genital anomalies of the biocatalytic type (functional bleeding, endometriosis, hyperplasia, psychosomatic symptoms), and constitutional anomalies (infantilism, cachexia, eunuchoid states, precocious puberty). There is fairly complete coverage of the subject of sexual deviations, and a rather rigid system of reduction diets is prescribed for obesity.

In his description of the specific diseases of the female genitals, Louros comes closest to general agreement with American ideas. He prefers the League of Nations Classification for classifying carcinoma of the cervix, however, and does not even mention the International Classification, an obviously regrettable circumstance. Louros is an advocate of radical operation for cervical carcinoma, but he insists that postoperative irradiation be given all patients so treated, and specifically decries Anglo-Saxon tendencies to the contrary. The section on contraception and sterilization is unusually liberal in attitude.

The final part of the work deals with the technique of gynecologic surgery. A short elementary instrumentarium is given, followed by a general section on incisions, methods of closure, and related topics. There follows a regional coverage of standard operations, and here the inferior quality of the illustrations, of limited importance in the other sections of the book, becomes a distinct liability. Many of the illustrations are copied from other authors; but there is also a liberal sprinkling of drawings by the author himself; the latter are of the sketchy and impressionistic type, lacking the clarity required in expository drawing. Most American gynecologists do not share Louros' reluctance to do vaginal hysterectomy; in effect, he relegates this operation to the realm of occasional gynecologic surgery. The author's favorite operation for the correction of genital prolapse is Kjelland's modification of the Watkins-Wertheim interposition procedure, which he maintains has been productive of excellent results in his hands. Although he lists only a relatively few indications for suspension of the uterus, suspension operations are elaborately described. Louros' views on total versus subtotal hysterectomy correspond in the main to American views on this subject. Considerable detail and several mediocre drawings are lavished on operations for salpingostomy. A useful section is that entitled by the author "Para-gynecologic Operations," including such things as Scheppelmann's operation for *Hängebauch*, herniorrhaphy, appendectomy, and repair of such operative injuries as may be encountered by the gynecologist. Enthusiasm will not run high for the author's suggestion that the operator who transects the ureter high in the pelvis should solve the problem by tying a knot in the proximal stump.

The final section on postoperative care conforms in general to United States practice except for the excessive reluctance of the author to give narcotics postoperatively for the control of pain.

The work is written in clear though slightly stilted French; its style is sometimes high flown, particularly in the sections dealing with psychobiologic topics. The book is nicely printed and sturdily bound. Its value to American gynecologists is naturally limited by both language and viewpoint, but it nevertheless presents the experience and practice of a contemporary gynecologist of stature.

Hypertension: Humoral and Neurogenic Factors. A Symposium. 294 pages with 73 illustrations. Boston, 1954, Little, Brown and Co. $6.75.

Thirty-three participants from 13 countries presented and discussed 21 papers dealing with some of the physiologic aspects of hypertension. Some of the papers are reviews, some are formal presentations of new data, some are progress reports, and some are speculative. The discussions are most interesting.

The book is well printed, although the five-page subject index is rather inadequate, particularly in reference to material in the discussions. This symposium can be recommended to anyone whose interest in the physiology of hypertension outweighs a reluctance to budget for expensive books.

The Biochemistry of Semen. By T. Mann. 240 pages with 23 illustrations. New York, 1954, John Wiley & Sons, Inc. $2.90.

This valuable book summarizes and tabulates a vast amount of data bearing upon the physiology and biochemistry of the semen and its constituents. The recorded studies range over the animal kingdom, with occasional allusions to the plant kingdom as well. There is a 28 page bibliography and a good index of 18 pages.

The text is so heavily documented as to make reading rather slow. While well printed, the type is small. The book probably will have a limited popularity but certainly it can be recommended as a fount of information. The writer is well known for his work in this field and he has produced an authoritative survey.

Christopher's Minor Surgery. By A. Ochsner and M. DeBakey. Seventh edition. 547 pages with 251 illustrations. Philadelphia, 1955, W. B. Saunders Company.

The fact that this classical volume has withstood the gauntlets of critical reviews in the course of the publication of six previous editions attests to its wide acceptance. This present edition should, on its own merit, enjoy even greater popularity.

Physicians engaged in general practice may frequently be faced with problems of minor surgery in any body system. Many techniques of treatment have effected satisfactory results in the past but are more efficiently handled using those methods proposed by the contributors. The specialist realizes that he cannot divorce the problems of his own forte from the other perhaps lesser difficulties outside his field which the patient may present to him while under his care. Even if he should not feel qualified or wish to treat the complaint he must be able to explain it and to make the correct referral. The authors have so clearly presented each topic that with the knowledge refreshed by reading either the book or the recommended references he may readily do this.

The scope of the writing is exceptional. There is a sound discussion not only of disease best treated by minor surgery of every system but equally thoughtful information is to be found concerning office equipment, anesthesia, and even surgical residencies.

A typical section is the one on the female genitourinary organs. This chapter is in no way meant to be a substitute for a text written specifically on this topic. Proper emphasis has been given, however, to diagnostic methods, cancer detection, and as to which common diseases may be treated in the office or the clinic and which require the hospitalization of the patient.

The Management of Obstetric Difficulties. By Paul Titus, revised by J. Robert Willson. Fifth edition. 737 pages with 348 illustrations. St. Louis, 1955, The C. V. Mosby Company.

The primary aim of the first edition was to develop a work of practical aid for the management of obstetric difficulties and emergencies. The present publication includes this principle although it is beginning to take the form of the conventional textbook on obstetrics.

The causes and treatment of infertility are discussed in Section 1. The techniques illustrated for insemination are not good and the apparatus described for tubal insufflation is not modern. In Section 2, the methods of diagnosis of pregnancy and prenatal care are described in succinct fashion. The sustained elevation of the basal body temperature might have been included as an early accurate diagnostic test for pregnancy. The complications of pregnancy are described in the third section. The authors state in their discussion on choriocarcinoma that pelvic surgery should be attempted even though pulmonary metastases are present. It is their opinion that these metastatic lesions often decrease in size or even disappear after removal of the primary growth although this impression is not corroborated by other reports in the literature. Perhaps the authors are referring to the metastatic lesion of chorioadenoma destruens. The chapter on bleeding in late pregnancy is presented with clarity. Toxemia of pregnancy is comprehensively discussed. The authors state that veratrum preparations are not indicated in the treatment of eclampsia. Recent publications, however, have shown a decrease in maternal mortality from eclampsia when Veratrone is combined with magnesium sulfate.

In the fourth section complications of labor are discussed. The authors caution against the use of Pituitrin in the third stage of labor if cyclopropane is employed. The causes and management of postpartum hemorrhage are cited in detail except for the role of coagulation defects. Obstetric operations are described clearly in Section 5. The authors do not mention their attitude toward trial forceps and the use of Barton forceps for rotation is omitted. In the sixth part of the book the normal puerperium and its complications are noted. Various types of obstetric analgesia and anesthesia are cited. The methods and purpose of special examination and treatments employed in obstetrics are emphasized. The newborn infant, its care during labor and at delivery, and neonatal diseases are described in the final section.

The references are recent but meager. There are several errors in the spelling of proper names and in the general text. The index is not sufficiently detailed. Several important recent advances in obstetrics such as coagulation defects, obstetric shock, vasodilator drugs in hypertension, and the role of cardiac surgery in rheumatic valvular disease are not thoroughly discussed.

The authors' style of writing is good. The illustrations are numerous and clear.

Items

American Board of Obstetrics and Gynecology, Inc.

The next scheduled examination (Part I), written examination and review of case histories, for all candidates will be held in various cities of the United States, Canada, and military centers outside the continental United States, on Friday, Feb. 3, 1956.

Case abstracts numbering 20 are to be sent by the candidate to the Secretary as soon as possible after receiving notification of eligibility to the Part I written examination.

ROBERT L. FAULKNER, M.D., SECRETARY
2105 ADELBERT ROAD
CLEVELAND 6, OHIO

International Fertility Association

The Second World Congress of the International Fertility Association will be held in Naples, May 18 to 26, 1956.

For further information write to Prof. G. Tesauro, S. Andrea delle Dame, 19, Naples, Italy.

A Residents Exchange Program With Great Britain

Exchange of residents between Great Britain and this country may be facilitated by a program of the Horse Shoe Club. This organization is composed of about 400 British, Canadian, and American doctors and was founded in 1932 for the purpose of fostering friendship and the exchange of medical, research, and clinical workers among the three countries. The Club is now prepared to work in the arrangements by which a resident in an American training program may be exchanged for one in a British program. The Club is prepared to assist in the placement of residents in general surgery and the surgical specialties.

The original plans call for an exchange of about one year's duration, the American resident usually being at the second or third year level. Those coming from Great Britain may be somewhat farther along in their training programs but would be fitted into the American residency so as to provide the best opportunity for training and experience. The host institution is expected to provide for the expense of living of the visiting student, but the travel expense is to be borne by the parent hospital.

It is hoped that those who are responsible for approved programs of training in general surgery and the surgical specialties in this country will consider the possibility of participation in this exchange program for the mutual benefit of members of the profession in Great Britain and the United States. Specific inquiry concerning the program should be addressed to the American College of Surgeons. It should be emphasized that this program does not interfere in any way with exchange programs that now exist or that may be established. Private arrangements made between schools and hospitals in both countries are all important and it is hoped that they will be amplified. Under these circumstances the Horse Shoe Club offers friendship and aid when needed to the Fellows in both countries.

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(Appears in January and July)

American Academy of Obstetrics and Gynecology. (1945) *President,* Ralph E. Campbell. *Secretary,* C. Paul Hodgkinson, 17546 Meadowood Ave., Birmingham, Mich. Next meeting, November, 1956.

American Gynecological Society. (1876) *President,* Isidor Clinton Rubin. *Secretary,* John I. Brewer, 104 S. Michigan Ave., Chicago 3, Ill. Next meeting, The Shoreham, Washington, D. C., May 21-23, 1956.

American Association of Obstetricians and Gynecologists. (1888) *President,* Lawrence M. Randall. *Secretary,* Frank R. Lock, Bowman Gray School of Medicine, Winston-Salem, N. C. Spring meeting, March 23 and 24, 1956. Annual meeting Sept. 6-8, 1956.

Central Association of Obstetricians and Gynecologists. (1929) *President,* Harold L. Gainey. *Secretary,* Edwin J. DeCosta, 104 S. Michigan Ave., Chicago 3, Ill. Annual meeting at New Orleans, La., Oct. 4, 5, and 6, 1956.

South Atlantic Association of Obstetricians and Gynecologists. (1938) *President,* Waverly R. Payne. *Secretary,* Charles H. Mauzy, Bowman Gray School of Medicine, Winston-Salem, N. C. Next meeting, Hollywood Beach Hotel, Hollywood Beach, Fla., Jan. 28-Feb. 1, 1956.

A. M. A. Section on Obstetrics and Gynecology. *Chairman,* Frank R. Lock. *Secretary,* D. Frank Kaltreider, University Hospital, Baltimore 1, Md. Meetings with annual A.M.A. meetings.

Society of Obstetricians and Gynaecologists of Canada. (1944) *President,* Rene Simard, Quebec City, Quebec. *Secretary,* F. P. McInnis, 280 Bloor St. W., Toronto, Ont. Next meeting, Manoir Richelieu, Murray Bay, Quebec, June 8-10, 1956.

Akron Obstetrical and Gynecological Society. (1946) *President,* Edward F. Hellwig. *Secretary,* Carl J. Paternite, 159 S. Main St., Akron, O. Meetings, quarterly.

Alabama Association of Obstetricians and Gynecologists. (1940) *President,* Joe W. Perry. *Secretary,* James H. French, 201 Montgomery St., Montgomery, Ala. Next meeting in Birmingham, Ala., April 18, 1956.

Alameda County Gynecological Society. (1951) *President,* Victor Koerper. *Secretary,* Wallace Lawson, 2975 Telegraph Ave., Berkeley 5, Calif. Meetings, fourth Wednesday of each month except June, July, August, and December.

Arkansas Obstetrical and Gynecological Society. (1953) *President,* John Walter Jones. *Secretary,* Robert W. Ross, 908 Donaghey Bldg., Little Rock, Ark. Meetings, May and October.

Atlanta Obstetrical and Gynecological Society. (1954) *President,* Charles B. Upshaw. *Secretary,* George A. Williams, Suite 6, 710 Peachtree St., N. E., Atlanta 8, Ga. Meetings quarterly.

Birmingham Obstetrical and Gynecological Society. (1949) *President,* Hunter Brown. *Secretary,* Clay Wells, 1908 8th Ave., South, Birmingham, Ala. Four meetings annually.

Boston, Obstetrical Society of. (1861) *President,* Duncan E. Reid. *Secretary,* A. Gordon Gauld, 1180 Beacon St., Brookline 46, Mass. Meetings, third Tuesday of October, November, January, February, and March.

Bronx Gynecological and Obstetrical Society. (1924) *President,* Alex Charlton. *Secretary,* John S. Giaccone, 1488 Metropolitan Ave., Bronx 62, N. Y. Meetings, fourth Monday, October through April, inclusive.

Brooklyn Gynecological Society. (1890) *President,* William Pomerance. *Secretary,* Leslie H. Tisdall, 615 Third St., Brooklyn 15, N. Y. Meetings, third Wednesday, October, November, January, February, March, April, and May.

Buffalo Obstetrical and Gynecological Society. (1946) *President,* Robert C. McDowell. *Secretary,* Louis A. Trippe, 511 Lafayette Ave., Buffalo 22, N. Y. Meetings, first Tuesday, October through May.

---

*Changes, omissions, and corrections should be sent to the publisher, The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Mo. The number after the Society's name is the year of founding. For further information, address the respective secretaries.

Central New York Association of Gynecologists and Obstetricians. (1938) ***President,*** Charles Gwynn. *Secretary,* William Redfield, 1502 State Tower Bldg., Syracuse 2, N. Y. Meetings, second Tuesday, January, March, May, September, and November.

Chicago Gynecological Society. (1878) *President,* Magnus P. Urnes. *Secretary,* Clyde J. Geiger, 4753 Broadway, Chicago 40, Ill. Meetings, third Friday, October through June.

Cincinnati Obstetrical Society. (1876) *President,* Richard D. Bryant. *Secretary,* John F. Mohan, 3731 St. Lawrence, Cincinnati 5. Meetings, third Thursday, September through May.

Cleveland Society of Obstetrics and Gynecology. (1947) *President,* O. B. Pomeroy. *Secretary,* Eduard Eichner, 10605 Chester Ave., Cleveland 6. Meetings, fourth Monday, September, November, January, March, and May.

Columbus Obstetric-Gynecologic Society. (1944) *President,* John H. Holzaepfel. *Secretary,* Fred B. Hapke, 350 E. Broad St., Columbus 15, Ohio. Meetings, last Wednesday of month, September through May.

Dallas-Fort Worth Obstetrical and Gynecological Society. (1948) *President,* D. G. Harrell. *Secretary,* H. I. Kantor, 3534 Maple Ave., Dallas, Texas. Meetings, spring and fall.

Dayton Obstetrical and Gynecological Society. (1937) *President,* W. K. Gregg. *Secretary,* Edward A. Millonig, 2300 Far Hills Ave., Dayton 9, Ohio. Meetings, third Wednesday, September through May.

Denver Gynecological and Obstetrical Society. (1942) *President,* E. Stewart Taylor. *Secretary,* Charles R. Freed, 1809 E. 18th Ave., Denver 18, Colo. Meetings, first Monday of every month, October through May, inclusive, unless otherwise notified.

El Paso County Obstetrical and Gynecological Society. (1948) ***President,*** **Erich Spier.** *Secretary,* Alvin L. Perry, 209 Medical Arts Bldg., El Paso, Texas. Meetings, last Thursday, every other month.

Florida Obstetric and Gynecologic Society. (1948) *President,* J. Champneys Taylor. *Secretary,* R. B. Chrisman, Jr., 356 Alhambra Circle, Coral Gables, Fla. Next meeting, Miami Beach, Fla., May 13, 1956.

Georgia State Obstetrical and Gynecological Society. (1951) *President,* O. R. Thompson. *Secretary,* J. Lon King, Jr., 817 Persons Bldg., Macon, Ga. Next meeting, May 13 and 14, 1956.

Harris, John Warton, Obstetrical Society. (1953) *President,* E. Russell Muntz. *Secretary,* Alice D. Watts, 324 E. Wisconsin Ave., Milwaukee 2, Wis. Next meeting, May 18, 1956.

Honolulu Obstetrical and Gynecological Society. (1947) *President,* Lyle Bachman. *Secretary,* Fugate Carty, Straub Clinic, Thomas Square, Honolulu, Hawaii. Meetings, third Monday of each month at the Mabel Smythe Memorial Bldg.

Houston Obstetrical and Gynecological Society. (1939) *President,* M. J. Meynier, Jr. *Secretary,* Thomas G. Gready, Jr., 608 Hermann Professional Bldg., Houston, Texas. Meetings, first Tuesday each month, October through June.

Indianapolis Obstetrical and Gynecological Society. (1947) *President,* Carl P. Huber. *Secretary,* John F. Spahr, Jr., Suite 902, 23 East Ohio St., Indianapolis 4. Meetings, second Wednesday in January, April, and October.

Interurban Obstetrical and Gynecological Society. (1949) *President,* Robert C. McDowell, Buffalo, N. Y. *Secretary,* E. R. Duggan, 16 N. Goodman St., Rochester 7, N. Y.

Iowa Obstetrical and Gynecological Society. *President,* L. G. Carrigg, Cedar Rapids, Iowa. *Secretary,* William C. Keettel, State University of Iowa Hospitals, Iowa City, Iowa. Meetings, April and November.

Kansas City Gynecological Society. (1922) *President,* Gerald L. Miller. *Secretary,* Floyd C. Atwell, 411 Nichols Rd., Kansas City 12, Mo. Meetings, third Thursday, September, November, January, and March, and first Thursday in May.

Kentucky Obstetrical and Gynecological Society. (1947) *President,* A. B. Barrett, Lexington, Ky. *Secretary,* R. C. Bateman, 432 W. Main St., Danville, Ky. Annual meeting, spring, 1956.

Los Angeles Obstetrical and Gynecological Society. (1914) *President,* Samuel Martins. *Secretary,* Walter C. Rogers, 39 Congress St., Pasadena 2, Calif. Meetings, second Tuesday, September, November, January, March, and May.

Louisville Obstetrical and Gynecological Society. *President,* J. O. H. Simrall. *Secretary,* Hugh P. Adkins, 920 Heyburn Bldg., Louisville 2, Ky. Meetings, fourth Monday, September, October, November, January, February, March, April, and May.

Madison Obstetrical and Gynecological Society. (1950) *President* and *Secretary,* Leonard J. McKenzie, 16 N. Carroll St., Madison, Wis. Meetings, first Tuesday each month except July and August.

Maryland, Obstetrical and Gynecological Society of. (1929) *President,* John Herman Long. *Secretary,* Harry M. Beck, 700 N. Charles St., Baltimore 1, Md. Meetings, second Thursday, October, December, February, and May.

Memphis Obstetrical and Gynecological Society. (1950) *President,* John J. Redmon. *Secretary,* William F. Mackey, 1374 Madison Ave., Memphis, Tenn. Meetings, second Tuesday, October, November, January, March, and May.

Miami Obstetrical and Gynecological Society. (1946) *President,* Richard F. Stover. *Secretary,* Richard C. Forman, 427 Biltmore Way, Coral Gables, Fla. Meetings, second Thursday, January, March, May, and November.

Michigan Society of Obstetricians and Gynecologists. (1924) *President,* John P. Attaway. *Secretary,* E. Bruce Foster, 853 Fisher Bldg., Detroit 2, Mich. Meetings, first Tuesday, October, November, December, February, March, April, and May.

Milwaukee Gynecological Society. (1951) *President,* William F. Hovis. *Secretary,* L. T. Servis, 425 East Wisconsin Ave., Milwaukee 2, Wis. Meetings, last Monday, January, March, May, and November.

Minnesota Obstetrical and Gynecological Society. *President,* Leonard A. Lang, Minneapolis, Minn. *Secretary,* Edward A. Banner, 200 First St., Southwest, Rochester, Minn. Meetings, spring and fall.

Mississippi Obstetrical and Gynecological Society. (1947) *President,* James L. Royals, Jackson, Miss. *Secretary,* J. A. K. Birchett, Jr., P.O. Box 367, Vicksburg, Miss. Meetings May and November.

Mobile County Obstetrical and Gynecological Society. (1949) *President,* H. B. Dowling. *Secretary,* J. R. Mighell, 1302 Government St., Mobile, Ala. Meetings, quarterly when called.

Montgomery County (Ohio) Obstetrical and Gynecological Society. (1937) *President,* L. O. Fredericks. *Secretary,* A. A. Kunnen, 406 Harries Bldg., Dayton, Ohio. Meetings, third Wednesday of each month.

Montana Obstetrical and Gynecological Society. (1946) *President,* David Gregory, Glasgow, Mont. *Secretary,* Frank Pickett, Box 107, Bozeman, Mont. Annual meeting in April.

Nashville Obstetrical and Gynecological Society. (1955) *President,* D. S. Bayer. *Secretary,* H. M. Pace, Jr., 606 Gallatin Rd., Nashville, Tenn. Four meetings per year from October to May.

Nassau Obstetrical Society. (1944) *President,* Gerald T. Lilly. *Secretary,* Andrew S. Sherwin, 64 Hilton Rd., Hempstead, N. Y. Meetings, second Monday, October, December, February, and April.

New England Obstetrical and Gynecological Society. (1929) *President,* Lewis P. James. *Secretary,* Carmi R. Alden, 270 Commonwealth Ave., Boston 16, Mass. Meetings, spring and fall.

New Haven Obstetrical and Gynecological Society. (1946) *President,* Robert M. Lewis. *Secretary,* Fred Gibson, 37 Trumbull St., New Haven, Conn. Meetings, third Tuesday, September, November, January, March, and May.

New Jersey Obstetrical and Gynecological Society. (1947) *President,* Benjamin Devers. *Secretary,* Paul Grossbard, 162 Lexington Ave., Passaic. Meetings, October and April.

New Mexico Obstetrical and Gynecological Society. (1947) *President,* M. D. Bivens. *Secretary,* J. W. Wiggins, 24 Medical Arts Square, Albuquerque. Meetings, quarterly.

New Orleans Gynecological and Obstetrical Society. (1924) *President,* Abe Golden. *Secretary,* Gordon Johnson, Browne-McHardy Clinic, 3636 St. Charles Ave., New Orleans, La. Five meetings per year.

New York Obstetrical Society. (1863) *President,* Morris A. Goldberger. *Secretary,* George L. Bowen, 101 East 74th St., New York 21, N. Y. Meetings, second Tuesday, October through May.

North Carolina Obstetrical and Gynecological Society. (1932) *President,* Adam Thorp. *Secretary,* Fleming Fuller. Meeting last week end in April.

North Dakota Society of Obstetrics and Gynecology. (1938) *President,* R. W. Rodgers. *Secretary,* John Gillam, 807 Broadway, Fargo, N. D. Meetings, spring and fall.

Northeastern New York Obstetrical and Gynecological Society. (1935) *President,* Arthur D. Hengerer, Albany, N. Y. *Secretary,* Raymond L. Rhodes, 15 W. Notre Dame St., Glens Falls, N. Y. Meetings, February, May, and October.

Oklahoma City Obstetrical and Gynecological Society. (1940) *President,* Robert D. McKee. *Secretary,* James B. Pitts, Jr., 313 Pasteur Medical Bldg., Oklahoma City, Okla. Meetings, February, April, May, October, and December.

Omaha Obstetrical and Gynecological Society. (1947) *President,* Leo T. Heywood. *Secretary,* W. Riley Kovar, 1120 Medical Arts Bldg., Omaha 2. Meetings, third Wednesday, January, March, May, September, and November.

Oregon Society of Obstetricians and Gynecologists. *President,* C. Louise Clancy. *Secretary,* Melvin W. Breese, 1340 S. E. 80th Ave., Portland 16, Ore. Meetings, third Friday, October through May, except December.

Pacific Coast Obstetrical and Gynecological Society. (1931) *President,* Donald G. Tollefson, Los Angeles, Calif. *Secretary,* Donald W. DeCarle, 2000 Van Ness Ave., San Francisco, Calif. Next meeting, Oct. 31-Nov. 3, 1956.

Pacific Northwest Obstetrical and Gynecological Association. (1947) *President,* J. E. Harrison. *Secretary,* Earl L. Hall, 1220 Central Ave., Great Falls, Mont. Meeting, Empress Hotel, Victoria, B. C., May 15-18, 1955.

Philadelphia, Obstetrical Society of. (1868) *President,* S. Leon Israel. *Secretary,* Paul A. Bowers, 2031 Locust St., Philadelphia 3, Pa. Meetings, first Thursday, October through May.

Pittsburgh Obstetrical and Gynecological Society. (1934) *President,* William E. Gibson. *Secretary,* John C. Hughes, Schenley Park Apts., Pittsburgh 13, Pa. Meetings, first Monday, October through May, except January.

Portland Society of Obstetricians and Gynecologists. (1928) *President,* Karl Martzloff. *Secretary,* James M. Whitely, 207 Medical Arts Bldg., Portland, Ore. Meetings, fourth Wednesday, September through May.

Queens Gynecological Society. (1948) *President,* George Schaefer. *Secretary,* Joseph A. Gaetane, 147-15 46th Ave., Flushing, N. Y. Meetings, second Wednesday, October, December, February, and April.

Rochester Obstetrical and Gynecological Society. (1939) *President,* Donald Kariher. *Secretary,* Joseph Cooney, 100 Simpson Rd., Rochester 17, N. Y. Meetings, February, April, June, October, and December.

St. Louis Gynecological Society. (1924) *President,* J. Russell Vaughan. *Secretary,* Eugene G. Hamilton, 8505 Delmar Blvd., St. Louis 24. Meetings, second Thursday, October, December, February, and April.

San Antonio Obstetrical and Gynecological Society. *President,* G. G. Passmore. *Secretary,* Frank M. Posey, Jr., 640 Moore Bldg., San Antonio. Meetings, first Monday of the month.

San Diego Gynecological Society. (1937) *President,* George H. Derieux. *Secretary,* Wilton Lewis, 525 Hawthorn, San Diego 1, Calif. Meetings, as announced.

San Francisco Gynecological Society. (1929) *President,* Ernest W. Page. *Secretary,* Edmund F. Anderson, 2445 Ocean Ave., San Francisco 27, Calif. Meetings, second Friday, October through April.

Seattle Gynecological Society. (1941) *President,* Albert Lee. *Secretary,* John Clancy, 1010 Boylston, Seattle 4, Wash. Meetings, third Wednesday of each month, except summer months.

South Carolina Obstetrical and Gynecological Society. (1946) *President,* Jack Parker. *Secretary,* Lawrence L. Hester, Jr., 16 Lucas St., Charleston 16, S. C. Meeting, spring.

Southwest Obstetrical and Gynecological Society. (1951) *President,* Hollis Brainard, Tucson, Ariz. *Secretary,* Zeph B. Campbell, 550 W. Thomas Rd., Phoenix, Ariz. Annual meeting, October, 1956.

Texas Association of Obstetricians and Gynecologists. (1930) *President,* John T. DeLaney, Galveston, Texas. *Secretary,* Oran V. Prejean, 4317 Oak Lawn Ave., Dallas 19, Texas. Annual meeting, Feb. 18, 1956.

Tulsa Obstetrical and Gynecological Society. (1955) *President,* D. N. Burns. *Secretary,* J. E. Goldberg. Five meetings per year.

Utah Obstetrical and Gynecological Society. (1948) *President,* Morgan S. Coombs. *Secretary,* Von G. Holbrook, 508 East South Temple, Salt Lake City 2. Meetings, second Tuesday of October, December, March, and May, or as announced.

Virginia Obstetrical and Gynecological Society. (1936) *President,* George S. Hurt. *Secretary,* Chester D. Bradley, 2914 West Ave., Newport News, Va. Meetings, April and October.

Washington Gynecological Society. (1933) *President,* Russel Jon Jansen. *Secretary,* Edmund F. Daley, 1835 Eye St., N. W., Washington 6, D. C. Meetings, last Saturday in October, November, January, March, and May.

Washington State Obstetrical Association. (1936) *President,* L. Bruce Donaldson. *Secretary,* Glen G. Rice, 805 Medical Dental Bldg., Seattle 1, Wash. Meetings, April 7, Oct. 20, 1956.

West Texas Obstetrical and Gynecological Society. (1954) *President,* O. R. Hand, Lubbock, Texas. *Secretary,* D. D. Wall, 234 W. Beauregard Ave., San Angelo, Texas. Meetings, twice yearly.

Wisconsin Society of Obstetrics and Gynecology. (1940) *President,* Dean D. Willson, Fond du Lac, Wis. *Secretary,* William V. Luetke, 1023 Regent St., Madison 5, Wis. Meetings, spring and fall.

FLORAQUIN VAGINITIS REGIMEN

New Intravaginal Applicator for Improved Treatment of Vaginitis

The restorative treatment of vaginitis with Floraquin is now further improved by a new aid to tablet insertion. Faulty insertion is no longer a failure factor in therapy.

The new Floraquin applicator is designed for simplified insertion of Floraquin tablets by the patient. This plunger device, made of smooth unbreakable plastic, places the Floraquin tablets in the fornices and thus assures coating of the entire vaginal mucosa as the tablets disintegrate. The patient inserts two Floraquin tablets with the applicator in the morning and also two tablets at night, with treatment being continued through at least two menstrual periods. During menstruation it is desirable to increase medication to eight tablets daily to combat the alkalinity of the menstrual flow.

Treatment with Floraquin tablets may be supplemented with insufflation of Floraquin powder by the physician. Frequency of insufflation is determined by the physician, but is of particular importance immediately following the patient's first menstrual period.

Warm acid douches (2 ounces of 5 per cent acetic acid or white vinegar to 2 quarts of warm water) may be taken as often as desired for hygienic purposes.

Floraquin contains Diodoquin® (diiodohydroxyquinoline, U.S.P.), the safe and effective protozoacide and fungicide. Lactose, anhydrous dextrose and boric acid are included to help restore the normal acid pH of the vaginal secretions. Such an acid vaginal medium then encourages the growth of normal flora and makes the environment unfavorable for pathogens.

A Floraquin applicator is supplied with each box of 50 (a new package size) Floraquin tablets. G. D. Searle & Co., Research in the Service of Medicine.

New Floraquin Applicator and clinical trial packages of Floraquin tablets are available on request to . . .

SEARLE

P. O. Box 5110, E-1
Chicago 80, Illinois

She adds her fancy:

she looks for its delicate yet firm texture, cleanly scented clarity, and soothing, gentle lubrication,

to your prescription facts:

full coating, occludes as it covers vaginal walls; optimal spreading for maximum coital mixing; greatest spermicidal opportunity; blandly protective of the entire mucosal area.

When contraception is indicated for young married couples.

LANTEEN®

JELLY

and Diaphragms

DISTRIBUTED BY GEORGE A. BREON & COMPANY, 1450 BROADWAY, NEW YORK 18, NEW YORK
IN CANADA: E. & A. HARTIN RESEARCH LTD., 20 RIPLEY AVE., TORONTO, CANADA
MANUFACTURED BY ESTA MEDICAL LABORATORIES, INC., CHICAGO 38, ILLINOIS

More Protection

for the prenatal patient

Stuart Prenatal

More B_{12}, more C, more iron, calcium from veal bone ash and calcium lactate plus all the important vitamins.

Dose: 1 to 3 tablets daily.
Bottles of 100 tablets.

Indianapolis M. D. Reports:

"Baby has no gas . . . seems more content with Steadifeed!"

HELPS PREVENT NURSING COLIC, GAS, EXCESSIVE BURPING.

Steadifeed's patented inner skirt stiffens nipple to prevent nipple collapse, air sucking and nursing colic. Many physicians, nurses, and mothers report Steadifeed better. Let Steadifeed solve your problems too!

Write for FREE Professional Sample

Babies Prefer

STEADIFEED

THE NIPPLE THAT B-R-E-A-T-H-E-S

SEARER RUBBER CO., Akron 4, Ohio

NIPPLES 10c
NURSERS 25c

END THE TORTURE

of agonizing vulvar itch in monilial vaginitis!

FAST, WELCOME RELIEF
HIGH RATE OF CURE

gentia·jel®

***Once* nightly — *just* 12 applications usually cures the most stubborn case**

GA-4

WESTWOOD PHARMACEUTICALS • Div. Foster-Milburn Co. • 468 Dewitt St., Buffalo 13, N. Y.

NEW *Simplified Control* of VAGINAL MYCOSIS

GENTIAN VIOLET SUPPRETTES
Contain: Gentian violet 0.2%
Lactic acid 0.3%
Acetic acid 1.0%
in Webster's exclusive Neocera base

WHAT IS "NEOCERA" BASE?
Consists of water-soluble Carbowaxes* with spreading agent . . . no oils or fatty materials. Breaks down in presence of moisture only. Releases medication completely and uniformly for total availability.

SUPPRETTE — SUCCESSOR TO THE SUPPOSITORY
Aspirin (Rectal administration)
Aspirin w/secobarbital sodium
Gentian 'E.V.' (Pinworms)
Aquachloral (Chloral hydrate for rectal administration)

*Trademark U.C.C.

IN
- *Pregnancy Moniliasis*
- *Antibiotic Mycosis*
- *Mycotic Leukorrhea*
- *Diabetic Vulvitis*
- *Mycotic Vulvovaginitis*
- *Pruritus Vulvae*

PHYSICIANS PREFER Gentian Violet Supprettes because maximum fungicidal activity is assured by thorough dispersion of the medication throughout the vaginal area.

PHYSICIANS PRESCRIBE Gentian Violet Supprettes because they provide rapid relief from itching, burning, local tenderness and discharge at less cost and with less mess to the patient than other gentian violet preparations.

EVEN the stubborn moniliasis frequently encountered during pregnancy or after antibiotic therapy quickly responds to treatment with Gentian Violet Supprettes.

New GENTIAN VIOLET *Supprettes*®
Simplified Control of Vaginal Mycosis

THE WILLIAM A. WEBSTER CO.
Memphis 3, Tennessee

PROFESSIONAL SAMPLES AVAILABLE ON REQUEST

Systemic Associations and Treatment of

SKIN DISEASES

By KURT WIENER, M.D.
Dermatologist, Mount Sinai Hospital, Deaconess Hospital, Saint Michael's Hospital, Milwaukee, Wisconsin

556 Pages, 90 Illustrative Plates

PRICE, $17.00

The author's earlier work entitled "Skin Manifestations of Internal Disorders" covered the skin changes which accompany internal or systemic diseases.

This new book looks in the opposite direction. It is concerned with the systemic phenomena associated with skin diseases.

The systemic, i.e., extracutaneous, relations of all skin diseases of importance such as eczema, psoriasis, urticaria, pemphigus, lupus erythematosus and many others are fully discussed.

The chapters on Systemic Therapy of skin diseases represent a third aspect of the complex which one might call systemic dermatology. Systemic therapy includes not only the nontopical drugs, but also diets, indirect radiation therapy and balneologic methods. Some light is also thrown on unorthodox methods.

The book is divided into two parts —Part One covering Systemic Associations of Skin Diseases; Part Two being devoted to Systemic Treatment of Skin Diseases. To a large degree the same pattern is followed in the discussion of each disease or condition. For example: In Part One the Incidence is first taken up, followed by the Systemic Relationship and Association, then Systemic Manifestations, Systemic Treatment. Frequently the Clinical Picture is given, along with the Prognosis, Pathology, Etiologic Factors, Diagnosis, Laboratory Findings—and, of course, details of Treatment. In Part Two the pattern is to discuss the Chemistry and Physiology, Clinical Application, Administration and Dosage, Side Effects, Results and Indications, Mode of Action, Toxicity, Precautions, Pharmacology and Contraindications.

THE C. V. MOSBY COMPANY
3207 Washington Blvd.
St. Louis 3, Missouri

Date _____

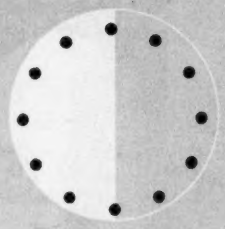
Gentlemen: Send me Wiener "SYSTEMIC ASSOCIATIONS AND TREATMENT OF SKIN DISEASES," priced at $17.00.

☐ Attached is my check. ☐ Charge my account.

Dr. _____ Street _____

City _____ Zone ____ State _____

AJOG—1-56



In 30 minutes–
antibacterial
action begins

In 24 hours–
turbid urine
usually clear

*"...it appears that Furadantin is one of the most effective single agents available at this time."**

Furadantin®

BRAND OF NITROFURANTOIN

IN URINARY TRACT INFECTIONS

- specific affinity for the urinary tract produces high antibacterial concentrations in urine in minutes—continuing for hours
- hundreds of thousands of patients treated safely and effectively
- rapidly effective against a wide range of gram-positive and gram-negative bacteria, including many strains of Proteus and Pseudomonas species and organisms resistant to other agents
- excellent tolerance—nontoxic to kidneys, liver and blood-forming organs
- no cases of monilial superinfection ever reported

SUPPLIED: Tablets, 50 and 100 mg. in bottles of 25 and 100.
Oral Suspension, 5 mg. per cc. bottle of 118 cc.

*Breakey, R. S.; Holt, S. H., and Siegel, D.:
J. Michigan M. Soc. *54*: 805, 1955.

EATON LABORATORIES, Norwich, N.Y. NITROFURANS a new class of antimicrobials neither antibiotics nor sulfas

More Protection
for the prenatal patient

Stuart Prenatal

More B_{12}, more C, more iron, calcium from veal bone ash and calcium lactate plus all the important vitamins.

Dose: 1 to 3 tablets daily.
Bottles of 100 tablets.

COLDS
SINUS
RESPIRATORY AILMENTS

THE NEW IMPROVED
VaporAll
VAPORIZER - INHALATOR
with AUTOMATIC CUTOFF
SAFE — EFFICIENT
3 Models for HOSPITAL, HOME or OFFICE
Send for Literature
SANIT-ALL PROD. CORP. Greenwich, Ohio

MEDICATED VAPOR
INHALATIONS
Runs up to
12 Hours

Booklet for patients

Your Care during Pregnancy

Practicing physicians are invited to ask for sample copy without obligation. Medically sponsored text. Used for a decade by thousands of leading doctors throughout United States and Canada. Write—

CADUCEUS PRESS
222 Nickels Arcade, Ann Arbor, Mich.

One out of three who died of cancer last year could have been saved!

To alert the practicing physician to suspect and diagnose cancer early—the American Cancer Society has available for you a film series of Physicians' Conferences on Cancer.

*Kinescopes of live, color, closed-circuit television programs, on early diagnosis and treatment of cancer, present outstanding clinicians.

These 24 film programs—the nucleus of a course on cancer for the General Practitioner—cover virtually all cancer sites and types. They center around panel discussions, laboratory techniques, case histories, x-ray findings, histopathology, statistical data, and operative procedures.

Professional Films and services available to the doctor in his own community may be obtained through your Division of the

American Cancer Society

* APPROVED BY THE AMERICAN ACADEMY OF GENERAL PRACTICE FOR INFORMAL STUDY CREDIT (16 MM COLOR SOUND FILMS. RUNNING TIME 30-50 MINUTES)

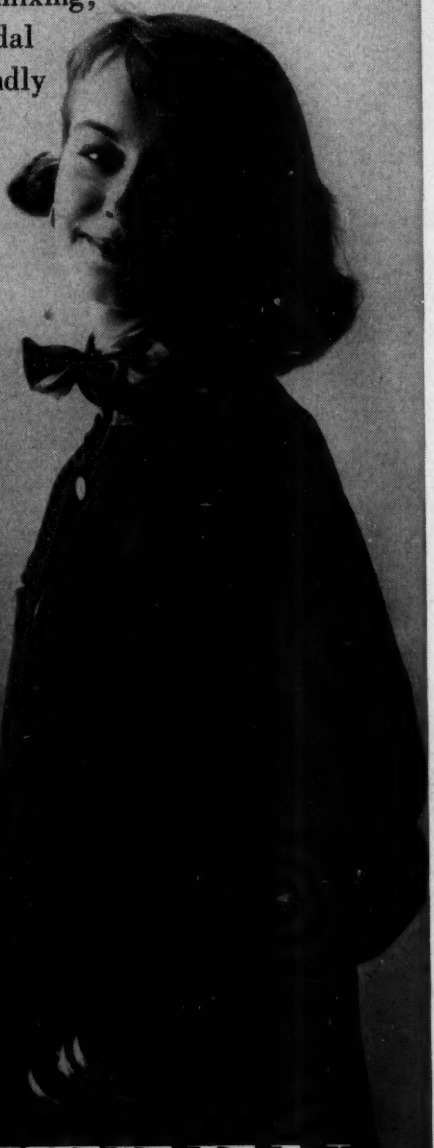
he adds her fancy:

she looks for its delicate yet
rm texture, cleanly scented clarity,
and soothing, gentle lubrication,

o your prescription facts:

ll coating, occludes as it covers
aginal walls; optimal spreading for
naximum coital mixing;
reatest spermicidal
pportunity; blandly
rotective of
he entire
ucosal area.

hen contraception
indicated for young
arried couples.



LANTEEN®
JELLY
and Diaphragms

DISTRIBUTED BY GEORGE A. BREON & COMPANY, 1450 BROADWAY, NEW YORK 18, NEW YORK
IN CANADA: E. & A. MARTIN RESEARCH LTD., 20 RIPLEY AVE., TORONTO, CANADA
MANUFACTURED BY ESTA MEDICAL LABORATORIES, INC., CHICAGO 38, ILLINOIS

For Security
SPECIFY.....

No Finer Name in Contraceptives...

Active Ingredients
Trioxymethylene 0.04%
Sodium Oleate 0.67%

WHITTAKER LABORATORIES, INC.
Peekskill, New York

for normal, healthy, comfortable pregnancies

Walker
500 CAPSULES
PRECALCIN®
LACTATE
A DIETARY SUPPLEMENT FOR USE DURING PREGNANCY AND LACTATION
EACH CAPSULE CONTAINS:
CALCIUM LACTATE, Anhydrous . . 450.00 mg.
VITAMIN A, Crystalline . . . 2,000 U.S.P. Units
VITAMIN D2, Crystalline . . 400 U.S.P. Units
THIAMINE HCl . . . . . 3.00 mg.
RIBOFLAVIN . . . . . 2.00 mg.
NIACINAMIDE . . . . . 10.00 mg.
ASCORBIC ACID . . . . . 30.00 mg.
CALCIUM PANTOTHENATE . . . . 2.50 mg.
PYRIDOXINE HCl . . . . . 1.00 mg.
FOLIC ACID . . . . . .33 mg.
VITAMIN B12 conc., activity equiv. to 1.00 mcg.
FERROUS GLUCONATE . . . . . 100.00 mg.
TRACE ELEMENTS*
*As Added Micronutrients
MICRONUTRIENTS
Copper (as Copper Sulfate) .2 mg.; Manganese (as Manganese Sulfate) .2 mg.; Cobalt (as Cobalt Sulfate) .04 mg.; Zinc (as Zinc Oxide) .2 mg.; Magnesium (as Magnesium Sulfate) .2 mg.; Molybdenum (as Sodium Molybdate) .04 mg.; Iodine (as Potassium Iodide) .02 mg.; and Fluorine (as Calcium Fluoride) .04 mg.
DOSE: 1 capsule three times daily, or as prescribed.
SEE CARTON FOR MINIMUM DAILY REQUIREMENTS AND OTHER INFORMATION
PRINTED IN U.S.A.
WALKER LABORATORIES, INC. · MOUNT VERNON, N. Y., U. S. A.

PHOSPHORUS-FREE, HIGH-POTENCY DRY-FILL* CAPSULES WITH "BUILT-IN" ANTIANEMIA FACTORS

*Micropulverized dry powder fill, for better toleration, faster assimilation and absence of fishy after-taste.

Walker LABORATORIES, INC., MOUNT VERNON, N. Y., U. S. A.

INDEX TO ADVERTISERS

Please mention "The American Journal of Obstetrics and Gynecology" when writing to advertisers—it identifies you

Abbott Laboratories ---- 17
American Cancer Society ---- 62
American Sterilizer ---- 11
Arnar-Stone Laboratories, Inc. ---- 16
Ayerst Laboratories ---- 38, 41, 54

Bard-Parker Co., Inc. ---- 35
Borden Co., The ---- Fourth Cover
Boyle & Co. ---- 48
Burroughs Wellcome & Co. (U.S.A.), Inc. 3

Caduceus Press ---- 62
Ciba Pharmaceutical Products, Inc. ---- 47
Ciba Pharmaceutical Products, Inc. ---- Second Cover

Davis & Geck, Inc. ---- Insert between pages 16 and 17
Desitin Chemical Co. ---- 18

Eaton Laboratories ---- 49, 61
Esta Medical Laboratories, Inc. ---- 58, 63
Ethicon, Inc. ---- Insert between pages 32 and 33

Florida Citrus Commission ---- 52

Gomco Surgical Manufacturing Corp. ---- 23
Grant Chemical Co., Inc. ---- 44

Hoffmann-La Roche, Inc. ---- Insert between pages 48 and 49
Hoffmann-La Roche, Inc. ---- 28
Holland-Rantos Co., Inc. ---- 51

Karger, S. ---- 46
Kidde Manufacturing Co. ---- 14
Kinney and Co., Inc. ---- 22

Lederle Laboratories ---- 43
Lilly and Co., Eli ---- 56
Lloyd Brothers, Inc. ---- 36, 37

McGraw-Hill Book Co., Inc., Blakiston Division ---- 24
Massengill Co., The S. E. ---- 21, 30, 31
Mead Johnson & Co. ---- 1

National Drug Co., The ---- 5, 34

O & G Instrument Co., Inc. ---- 2
Organon, Inc. ---- 7
Ortho Pharmaceutical Corporation ---- 45, 55

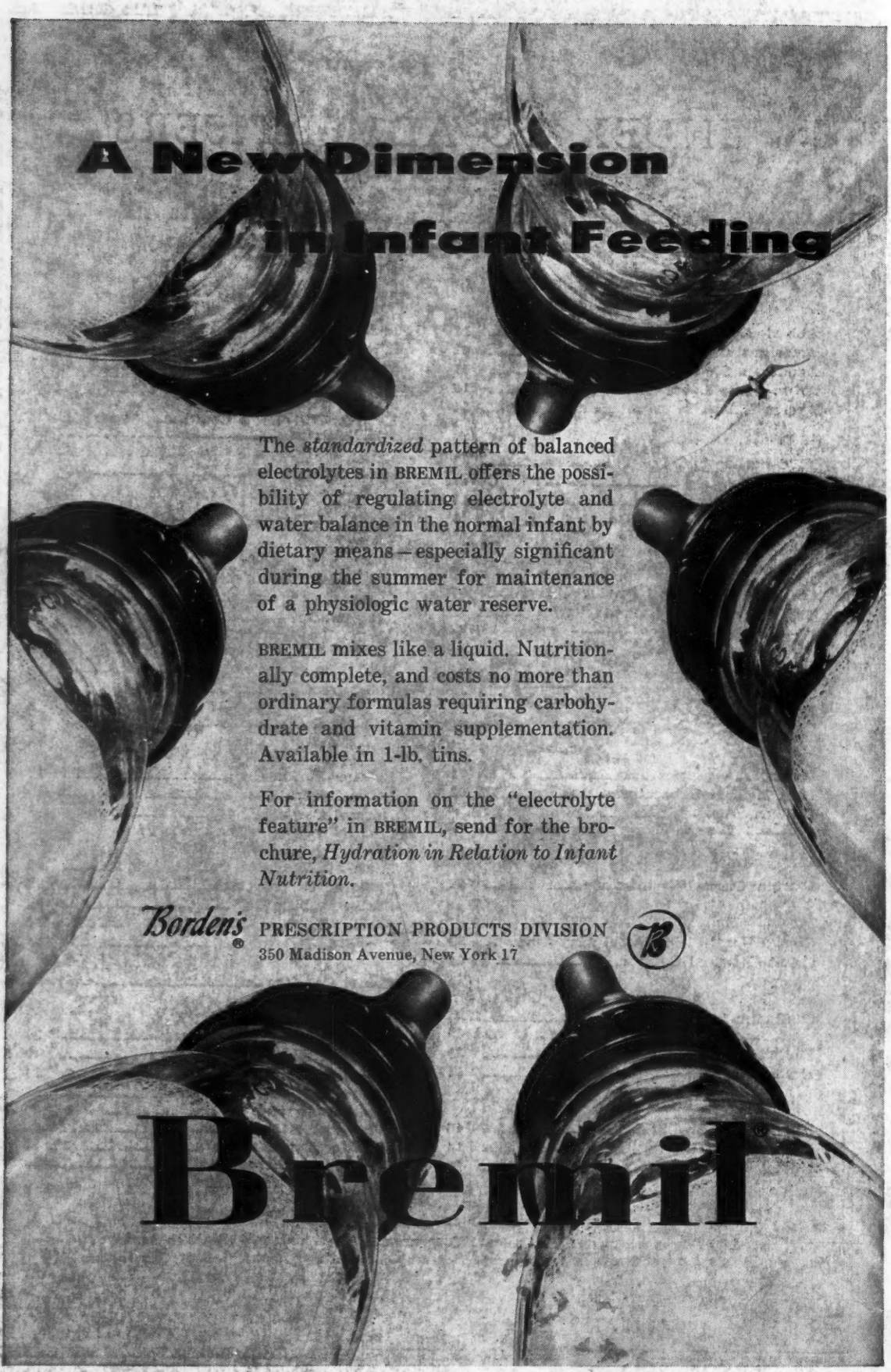
Parke, Davis & Co. ---- 25
Pet Milk Co. ---- 32
Pfizer Laboratories—Division of Chas. Pfizer & Co., Inc. ---- 29, 53

Ralston Purina Co. ---- 12
Riker Laboratories ---- 50
Roussel Corporation ---- 15

Sanit-All Products Corporation ---- 62
Schering Corporation ---- 33
Searer Rubber Co. ---- 58
Searle & Co. ---- 57
Sharp & Dohme ---- 39
Smith, Kline & French Laboratories 13, 42
Stuart Co., The ---- 58, 62

Walker Laboratories, Inc. ---- 64
Warner-Chilcott Laboratories ---- 9
Webster Co., The William A. ---- 59
Westwood Pharmaceuticals ---- 59
White Laboratories, Inc. ---- 4, 10, 20
Whittaker Laboratories, Inc. ---- 63
Whittier Laboratories ---- 26, 27
Winthrop Laboratories ---- 19

While every precaution is taken to insure accuracy, we cannot guarantee against the possibility of an occasional change or omission in the preparation of this index.


A New Dimension
in Infant Feeding
The *standardized* pattern of balanced electrolytes in BREMIL offers the possibility of regulating electrolyte and water balance in the normal infant by dietary means—especially significant during the summer for maintenance of a physiologic water reserve.
BREMIL mixes like a liquid. Nutritionally complete, and costs no more than ordinary formulas requiring carbohydrate and vitamin supplementation. Available in 1-lb. tins.
For information on the "electrolyte feature" in BREMIL, send for the brochure, *Hydration in Relation to Infant Nutrition.*
Borden's
PRESCRIPTION PRODUCTS DIVISION
350 Madison Avenue, New York 17
Bremil